

# EXHIBIT A



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(54) **VECTOR ENCODING HUMAN GLOBIN GENE AND USE THEREOF IN TREATMENT OF HEMOGLOBINOPATHIES**

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(52) **U.S. Cl.** ..... **435/320.1; 435/69.1; 536/24.1; 536/24.2; 424/93.2**

(58) **Field of Classification Search** ..... 435/320.1  
See application file for complete search history.

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(57) **ABSTRACT**

Recombinant lentiviral vectors having a region encoding a functional β-globin gene; and large portions of the β-globin locus control regions which include DNase I hypersensitive sites HS2, HS3 and HS4 provides expression of β-globin when introduced into a mammal, for example a human, in vivo. Optionally, the vector further includes a region encoding a dihydrofolate reductase. The vector may be used in treatment of hemoglobinopathies, including β-thalassemia and sickle-cell disease. For example, hematopoietic progenitor or stem cells may be transformed ex vivo and then restored to the patient. Selection processes may be used to increase the percentage of transformed cells in the returned population. For example, a selection marker which makes transformed cells more drug resistant than un-transformed cells allows selection by treatment of the cells with the corresponding drug.

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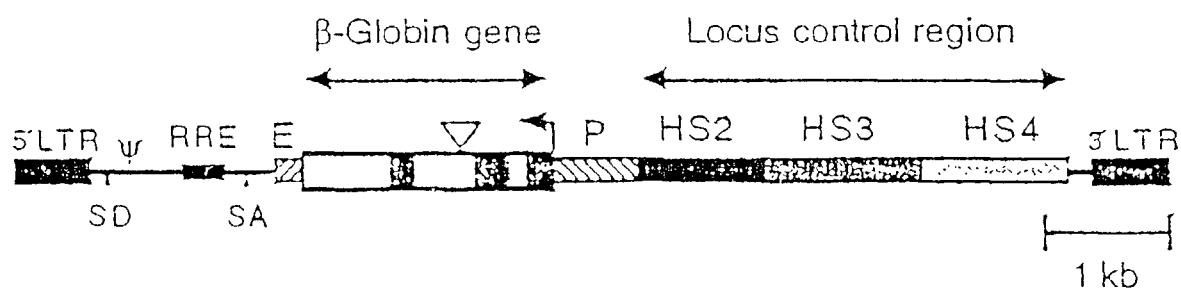
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**Fig. 1**

# Clinical Use of Drug Resistance

## In Vivo Selection of Genetically Modified Stem Cells

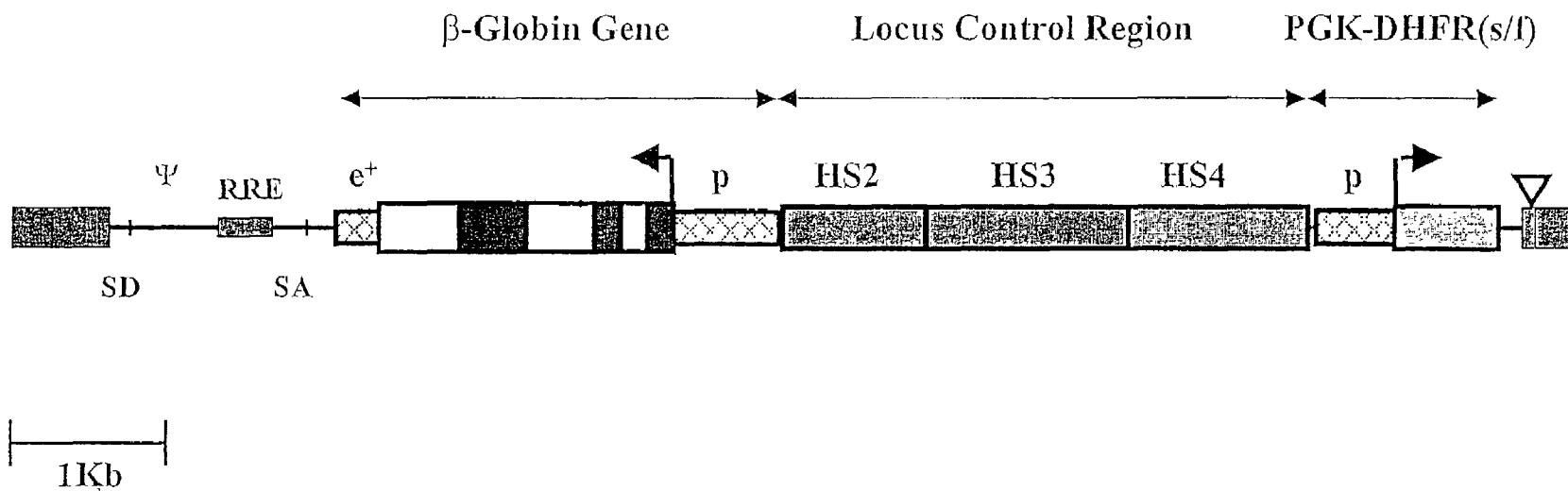


Fig. 2

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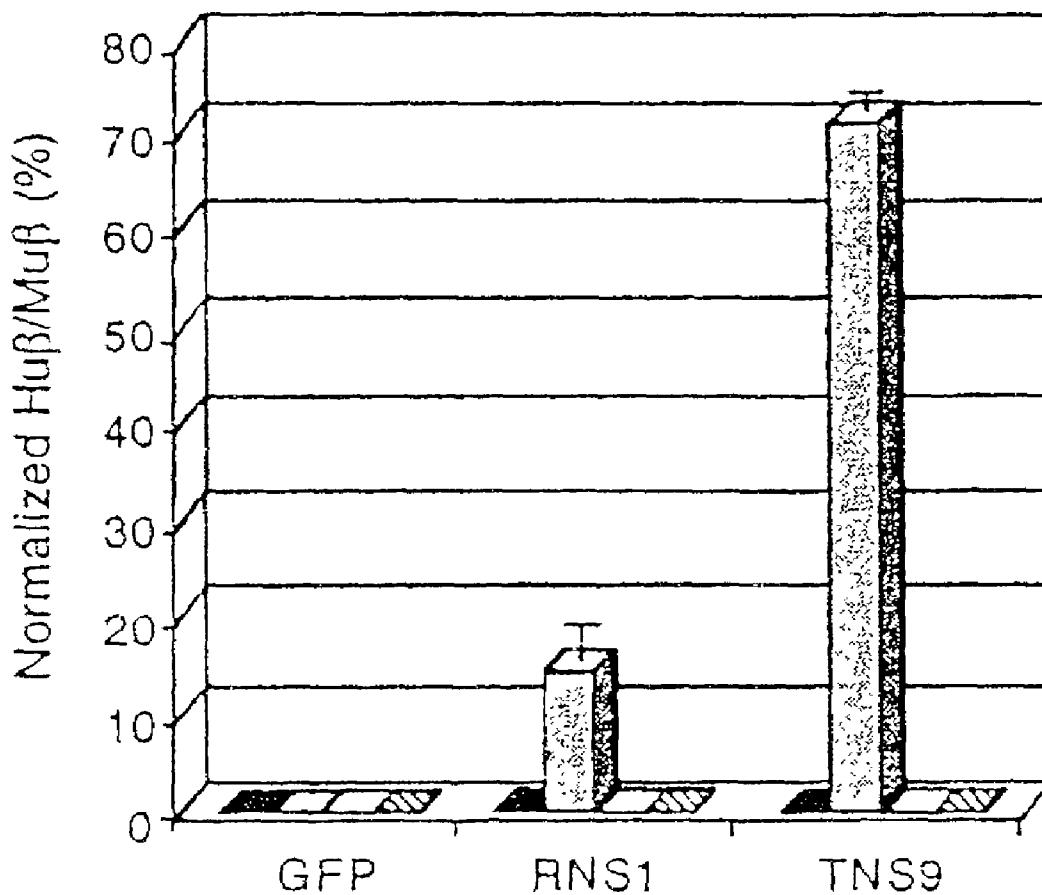


Fig. 3

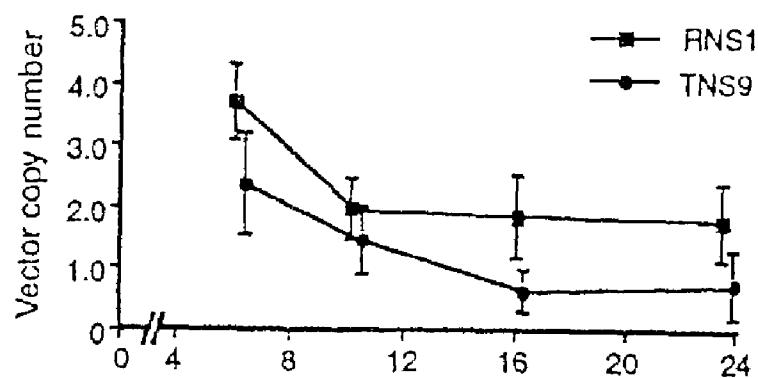


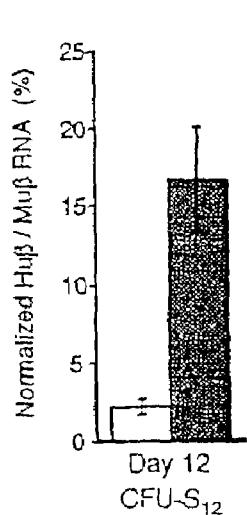
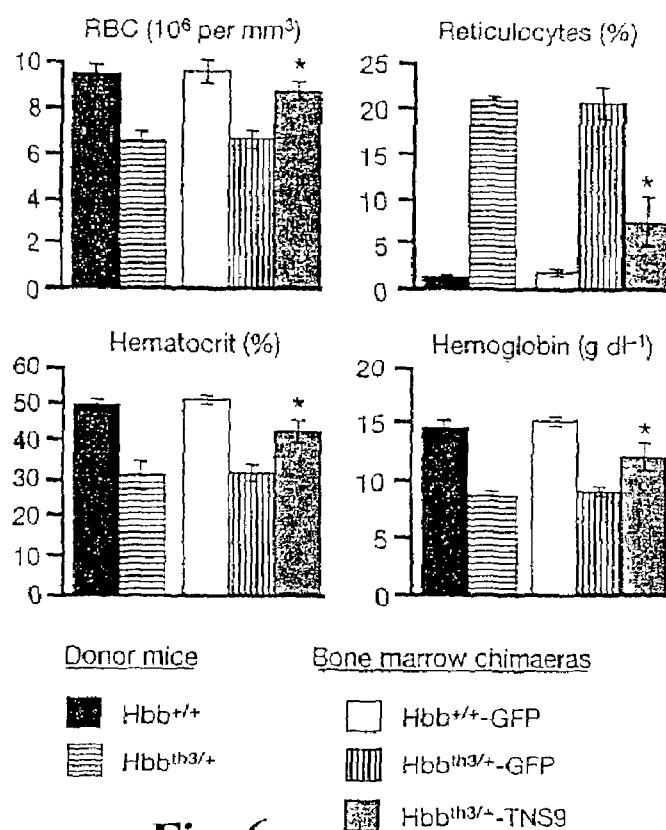
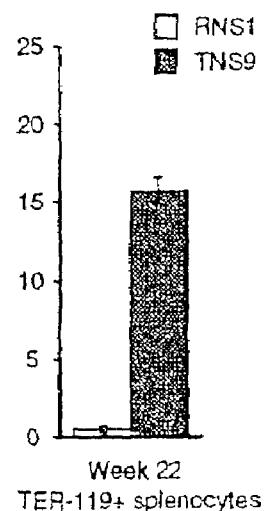
Fig. 4

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**Fig. 5 A****Fig. 5 B****Fig. 6**

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**VECTOR ENCODING HUMAN GLOBIN  
GENE AND USE THEREOF IN TREATMENT  
OF HEMOGLOBINOPATHIES**

**STATEMENT CONCERNING RELATED  
APPLICATIONS**

This application claims the benefit of U.S. Provisional Application No. 60/301,861 filed Jun. 29, 2001 and U.S. Provisional Application No. 60/302,852 filed Jul. 2, 2001, both of which are incorporated herein by reference.

**STATEMENT CONCERNING GOVERNMENT  
FUNDING**

This application was supported by funds provided under NHLBI grant No. HL57612. The United States government may have certain rights in the invention.

**BACKGROUND OF THE INVENTION**

This application relates to a vector comprising a mammalian, and particularly a human globin gene and to the use thereof in treatment of hemoglobinopathies, including  $\alpha$ - and  $\beta$ -thalassemia and sickle-cell disease.

Current treatment modalities for  $\beta$ -thalassemias consist of either red blood cell transfusion plus iron chelation (which extends survival but is cumbersome, expensive and an imperfect therapy), or allogeneic bone marrow transplant (which carries a lethal risk and is not available to the majority of patients). Thus, there is a substantial need for improved therapeutic approaches. The present invention provides a genetic correction in autologous hematopoietic stem cells, thus using gene therapy to provide a less-risky and more effective long-term treatment.

While gene therapy has been proposed for many years, a significant challenge facing efforts to develop gene therapy vectors is the ability to produce therapeutically useful levels of a desired protein or peptide. The present invention provides a vector which is capable of providing therapeutically meaningful levels of human globin for sustained periods of time. This ability arises from the ability to transmit large genomic regulatory sequences that control expression of the therapeutic gene.

**SUMMARY OF THE INVENTION**

In accordance with the invention, a recombinant lentiviral vector is provided comprising:

- (a) a region comprising a functional globin gene; and
- (b) large portions of the  $\beta$ -globin locus control regions which include large portions of DNase I hypersensitive sites HS2, HS3 and HS4. The regions may be the complete site or some lesser site which provides the same functionality as the specific sequences set forth below. This vector provides expression of  $\beta$ -globin when introduced into a mammal, for example a human, *in vivo*. Optionally, the vector further comprises a region encoding a dihydrofolate reductase.

By incorporation of different globin genes, the vector of the invention may be used in treatment of hemoglobinopathies, including  $\alpha$ - and  $\beta$ -thalassemia and sickle-cell disease. For example, hematopoietic progenitor or stem cells may be transformed *ex vivo* and then restored to the patient. Selection processes may be used to increase the percentage of transformed cells in the returned population. For example, a selection marker which makes transformed cells more drug resis-

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tant than un-transformed cells allows selection by treatment of the cells with the corresponding drug. Selection and/or enrichment may also be carried out *in vivo*, for example using methotrexate or similar antifolates to select for cells rendered resistant by the expression from the vector of a dihydrofolate reductase (DHFR).

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 shows the genomic structure of a recombinant onco-retroviral vector in accordance with the invention.

FIG. 2 shows the genomic structure of recombinant onco-retroviral vector within the scope of the invention.

FIG. 3 shows experimental results demonstrating increased mean  $\beta$ -globin expression in transduced MEL cells.

FIG. 4 shows the average vector copy number in peripheral blood cells, measured periodically for 24 weeks, which confirms highly efficient gene transfer in cells transduced with the vector of the invention.

FIGS. 5A and B show human  $\beta$ -globin expression per endogenous allele 12 days and 22 weeks after introduction of cells transduced with the vector of the invention.

FIG. 6 shows haematocrit level, red blood cell count, reticulocyte count and haemoglobin level fifteen weeks after transplantation with unselected TNS9-transduced  $Hbb^{th3/+}$  bone marrow.

**DETAILED DESCRIPTION OF THE INVENTION**

In a first aspect of the present invention, a recombinant lentiviral vector is provided comprising:

- (a) a region comprising a functional globin gene; and
- (b) large portions of the  $\beta$ -globin locus control regions, which include DNase I hypersensitive sites HS2, HS3 and HS4.

As used in the specification and claims hereof, the term "recombinant lentiviral vector" refers to an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation.

The term "functional globin gene" refers to a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with

a defective globin gene. The functional globin gene may encode a wild-type globin appropriate for a mammalian individual to be treated, or it may be a mutant form of globin, preferably one which provides for superior properties, for example superior oxygen transport properties. The functional globin gene includes both exons and introns, as well as globin promoters and splice donors/acceptors. Suitably, the globin gene may encode  $\alpha$ -globin,  $\beta$ -globin, or  $\gamma$ -globin.  $\beta$ -globin promoters may be used with each of the globin genes.

The recombinant vectors of the invention also include large portions of the locus control region (LCR) which include DNase I hypersensitive sites HS2, HS3 and HS4. In prior studies, smaller nucleotide fragments spanning the core portions of HS2, HS3 and HS4 have been utilized. Sadelain et al. *Proc. Nat'l Acad. Sci. (USA)*92: 6728-6732 (1995); Lebouich et al., *EMBO J.* 13: 3065-3076 (1994). The term "large portions" refers to portions of the locus control region which encompass larger portions of the hypersensitive sites as opposed to previously tested fragments including only the core elements. The regions may be the complete site or some lesser site which provides the same functionality as the specific sequences set forth below. In preferred embodiments of the invention, the large portions of the locus control regions

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are assembled from multiple fragments, each spanning one of the DNase I hypersensitive sites. In addition, the locus control region has two introduced GATA-1 binding sites at the junction between HS3 and HS4. While not intending to be bound by any specific mechanism, it is believed that the incorporation of these transcription factor binding sites enhances the effectiveness of the vector.

The genomic structure of one embodiment of the vector of the invention (TNS9) is shown in FIG. 1. TNS9 incorporates human β-globin gene (from position -618 to +2484) that includes an extended promoter sequence and a 3'-enhancer element. Optionally, a portion of 3'U3 region of the lentiviral backbone can be deleted for increased safety. In FIG. 1, the exons and introns of the human β-globin gene are represented by filled and open boxes. The locations are indicated for the splice donor (SD), splice acceptor (SA), packaging region ( $\Psi$ ), rev-response element (RRE), human β-globin promoter (P) and 3'-β-globin enhancer (E). Thus, in the vector TNS9, a functional β-globin gene, which includes both the exons and introns of the gene and the relevant control sequences from the human β-globin locus. These are combined with the large fragments of the locus control region. The 3.2 kb LCR assembled into dTNS9 consists of an 840 bp HS2 fragment (SnaBI-BstXI), a 1308 bp HS3 fragment (HindIII-BamHI) and a 1069 bp HS4 fragment (BamHI-BanII).

In a further aspect of the invention, the β-globin gene coding sequence can be exchanged and replaced with either the gamma globin gene (for sickle cell disease) or the alpha globin gene (for alpha-thalassemias). In one strategy, a NcoI-PstI fragment of the β-globin gene is replaced with the corresponding NcoI-HindIII fragment of the gamma globin gene or the NcoI-PstI fragment of the human alpha globin gene. These fragments start at the translational start of each globin gene (spanning the NcoI site) and end past their respective polyadenylation signals. In the second strategy, chimeric genes can be generated by only swapping the coding sequence of each one of the three exons of these genes. Thus, for the gamma globin gene, the result is a vector that comprises the beta globin promoter, the beta globin 5' untranslated region, the gamma exon 1 coding region, the gamma intron 1 the gamma exon 2, the beta intron 2, the gamma exon 3, and the beta 3' untranslated region. Thus all the elements of the TNS9 vector remain in place (promoter, enhancers, 5' and 3' untranslated regions, the LCR elements, the 2 additional GATA-1 binding sites and the introns of the beta globin gene (at least intron 2, which is most important). In a third strategy, the codon usage within exon 3 of the gamma globin gene can be modified so that its sequence will resemble as much as possible that of the beta globin gene. The reason for testing this is that the beta globin gene is always the best expressed<sup>1</sup>.

Additional elements may be included in the vectors of the invention to facilitate utilization of the vector in therapy. For example, the vector may include selectable markers, to confirm the expression of the vector or to provide a basis for selection of transformed cells over untransformed cells, or control markers which allow targeted disruption of transformed cells, and thus the selective removal of such cells should termination of therapy become necessary.

In a further specific embodiment, the vector of the invention includes the mouse PGK promoter and human dihydrofolate reductase (DHFR) cDNA as a transcriptional unit. Mutant forms of DHFR which increase the capacity of the DHFR to confer resistance to drugs such as methotrexate are suitably used. For example, single and double mutants of DHFR with mutations at amino acids 22 and 31 as described

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in commonly assigned PCT Publication No. WO 97/33988, which is incorporated herein by reference, may be advantageously utilized.

FIG. 2 shows the genomic structure of specific vector 5 within the scope of the invention. The vector includes a deleted LTR, from -456 to -9 of HIV LTR and the PGK promoter (530 bp) from the murine phosphoglycerate kinase 1 gene. It also includes a DHFR-encoding region encoding 10 human DHFR with s/f mutation at amino acid 22. The locus control region and the β-globin region are the same as in 15 TSN9. This vector is designated dTNS9-PD. This incorporation of DHFR into this vector provides transformed cells with a methotrexate-resistant phenotype. As a result, methotrexate, and other antifolates can be used, both in vitro and in vivo 20 as a selection tool to enhance levels of the functional hemoglobin. When hematopoietic stem cells were transformed using dTNS9-PD and reintroduced to mice that were then treated with NMBPR-P (0.5 mg/dose) and TMTX (0.5 mg dose) for five days, observed levels of expressed human 25 β-globin were much higher in mice transduced with dTNS9-PD vectors after treatment with TMTX and NMBPR-P for selection of transduced cells.

The vectors of the invention are used in therapy for treatment of individuals suffering from hemoglobinopathies. In 25 one embodiment of the invention, hematopoietic progenitor or stem cells are transformed ex vivo and then restored to the patient. As used in the specification and claims hereof, the term "hematopoietic progenitor and stem cells" encompasses hematopoietic cells and non-hematopoietic stem cells, 30 e.g., embryonic stem cells, hematopoietic stem cell precursors, or any of the latter generated by nuclear transfer from a somatic cell. It is known in the art that efficient gene transfer into human embryonic stem cells can be achieved using lentiviral vectors.

Selection processes may be used to increase the percentage 35 of transformed cells in the returned population. For example, a selection marker which makes transformed cells more drug resistant than un-transformed cells allows selection by treatment of the cells with the corresponding drug. When DHFR is 40 used as a selection marker, it can be used for enrichment of transduced cells in vitro, or for in vivo selection to maintain the effectiveness of the vector.

The invention will now be further described with reference 45 to the following non-limiting examples.

## EXAMPLE 1

To produce vector TNS9, the human β-globin gene was 50 subcloned from Mβ6L (Sadelain et al. *Proc. Nat'l Acad. Sci. (USA)* 92: 6728-6732 (1995)) into lentiviral vector pHRLacZ (Zuffery et al., *Nature* 15: 871-875 (1997)) replacing the CMV-LacZ sequence. pHRLegFP was constructed by replacing LacZ with the eGFP sequence (Clontech). Viral stocks 55 were generated by triple transfection of the recombinant vectors pCMVΔR8.9 (Zuffrey et al.) and pMD.G in 293T cells as previously described in Dull, et al., *J. Virol.* 72: 8463-8471 (1998). The pseudotyped virions were concentrated by ultracentrifugation resuspended and titrated as described in Galardo et al., *Blood* 90: 952-957 (1997). For comparison, RSN1 60 was used which has a similar structure, except that the LCR contains only the core portion of HS2, HS3 and HS4. Northern blot analysis showed full length RNA transcripts, indicating that the recombinant lentiviral genomes are stable. Southern blot analysis on genomic DNA from transduced 65 cells, digested once in each long terminal repeat (LTR) results in a single band corresponding to the expected size for the vector, indicating that the proviral structure is not rearranged.

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## EXAMPLE 2

To investigate the tissue specificity, stage specificity and expression level of the vector-encoded human  $\beta$ -globin gene, we transduced RNS1 and TNS9 into MEL cells, lymphoid Jurkat cells and myeloid HL-60 cells. Cell-free viral supernatant was used to infect C88 MEL cells in the presence of polybrene ( $8 \mu\text{g ml}^{-1}$ ). Transduced MEL cells were subcloned by limiting dilution, and screened by PCR for transduction<sup>30</sup> using primers that anneal in the human  $\beta$ -globin promoter sequence ( $\beta$ PS, 5'-GTCTAACAGTGATGACAGC-CGTACCTG-3', Seq ID No.: 1) and in HS2 (C2A, 5'-TCAGCCTAGAGT GATGACTCC TATCTG-3', Seq ID No.: 2). Vector copy number and integration site analysis was determined by Southern blot analysis<sup>9</sup>. Transduced MEL cells were induced to maturation by 5-day culture in 5 mM N,N'-hexamethylene bisacetamide (HMBA, Sigma).

To induce  $\beta$ -globin transcription, transduced MEL cell pools were differentiated using hexamethylene bisacetamide (HMBA). Human  $\beta$ -globin ( $\beta^4$ ) and mouse  $\beta$ -globin transcripts were measured by quantitative primer extension. After normalization to vector copy number and to endogenous  $\beta$ -globin expression per allele, human  $\beta$ -globin levels were  $14.2 \pm 4.7\%$  for RNS1 and  $71.3 \pm 2.3\%$  for TNS9 in pooled MEL cells (FIG. 2a). MEL, Jurkat and HL-60 cells were transduced with RNS1, TNS9 or control GFP recombinant lentivirus. Human  $\beta$ -globin RNA expression in HMBA induced MEL cells (grey bars) was measured by quantitative primer extension and normalized to mouse  $\beta$ -globin RNA expression per locus. Expression was then normalized to the vector copy number determined by Southern blot. No human  $\beta$ -globin RNA expression was detected in non-induced MEL (black bars), Jurkat (white bars) or HL-60 cells (hatched bars), indicating that globin expression was erythroid- and differentiation-specific. No human  $\beta$ -globin expression was detected in non-induced MEL, Jurkat and HL-60 cells (FIG. 3), indicating that human  $\beta$ -globin expression was appropriately regulated in terms of tissue specificity and state of differentiation. We generated a panel of MEL cell clones that carried a single copy of either vector to distinguish whether the increased expression obtained in HMBA-treated Mel cells transduced with TNS9 rather than RNS1 was the result of an increase in  $\beta^4$  expression per cell or of an increase in the fraction of cells expressing human  $\beta$ -globin. Transduced MEL cells were subcloned by limiting dilution immediately after transduction, avoiding any bias towards favourable chromosomal integration sites as produced by drug selection<sup>5</sup>. The proportion of clones expressing human  $\beta$ -globin varied significantly between the two vectors. One out of ten RNS1 positive clones yielded measurable human  $\beta$ -globin transcripts, in contrast to 12 out of 12 for TNS9 also expressed higher levels of human  $\beta$ -globin than did those bearing RNS1 ( $P < 0.01$ , Fisher's exact test). Cells bearing TNS9 also expressed higher levels of human  $\beta$ -globin than did those bearing RNS1 ( $P < 0.01$ , Wilcoxon rank sum test). These findings established that both the level and probability of expression at random integration sites was increased with the TNS9 vector.

## EXAMPLE 3

Quantification of Human  $\beta$ -globin mRNA

Total RNA was extracted from MEL, Jurkat and HL-60 cells, or mouse spleen and blood using TRIzol. Quantitative primer extension assays were done using the Primer Extension System-AMV Reverse Transcriptase kit (Promega) with [ $^{32}\text{P}$ ] dATP end-labelled primers specific for retroviral-de-

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rived human  $\beta$ -globin (5'-CAGTAACGGCAGACTTCTC-CTC-3', Seq ID No.: 3) and mouse  $\beta$ -globin (5'-TGATGTCT-GTTTCTGGGGTT GTG-3', Seq ID No.: 4), with predicted extension products of 90 bp and 53 bp, respectively. The probes yield products of identical length for  $\beta^{\text{maj}}$ ,  $\beta^{\text{min}}$ ,  $\beta^s$  and  $\beta'$ . Primers were annealed to 4  $\mu\text{g}$  of RNA and reactions were run according to manufacturer's protocols. Radioactive bands were quantitated by phosphorimager analysis (Bio-Rad). RNA isolated from A85.68 mice<sup>20</sup> was used as positive control. After correction for primer labelling, the human to mouse RNA signal was  $29 \pm 1\%$  per gene copy in repeated experiments ( $n > 8$ ), in agreement with previous findings based on RT-PCR<sup>20</sup>. Values measured in bone marrow chimaeras that were obtained in separate runs were standardized to the value obtained in the A85.68 RNA sample. In FIGS. 2 and 3c, d, human  $\beta$ -globin expression is expressed per vector copy and normalized to the endogenous transcripts (accounting for two endogenous alleles). In FIG. 3b, human transcripts are reported as the fraction of total  $\beta$ -globin RNA ( $\text{Hu}\beta/\text{Hu}\beta + \text{Mu}\beta$ ) to reflect absolute contribution of vector-encoded transcripts.

## EXAMPLE 4

To investigate the function of the vectors *in vivo*, we transduced and transplanted murine bone marrow cells without any selection in syngeneic, lethally irradiated recipient mice. Donor bone marrow was flushed from the femurs of 8- to 16-week-old male C57BL/6 or  $\text{Hbb}^{\text{th3/+}}\text{mice}$  (Jackson Laboratories) that had been injected intravenously (i.v.) 6 days earlier with 5-fluorouracil (5-FU, Pharmacia; 150 mg  $\text{kg}^{-1}$  body weight). Bone marrow cells were resuspended in serum-free medium, and supplemented with IL-1 $\alpha$  (10 ng  $\text{ml}^{-1}$ ), IL-3 (100 U  $\text{ml}^{-1}$ ), IL-6 (150 U  $\text{ml}^{-1}$ ), Kit ligand (10 ng  $\text{ml}^{-1}$ ) (Genzyme),  $\beta$ -mercaptoethanol (0.5 mM; Sigma), L-glutamine (200 mM), penicillin (100 IU  $\text{ml}^{-1}$ ) and streptomycin (100  $\mu\text{g ml}^{-1}$ ), and cultured for 18 h. Recipient mice (11- to 14-week-old C57BL/6 or  $\text{Hbb}^{\text{th3/+}}$  mice) were irradiated with 10.5 Gy (split dose  $2 \times 5.25$  Gy) on the day of transplantation. Bone marrow cells were pelleted and resuspended in serum-free medium containing concentrated lentiviral supernatant, and supplemented with polybrene (8  $\mu\text{g ml}^{-1}$ ), L-glutamine (200 mM), penicillin (100 IU  $\text{ml}^{-1}$ ) and streptomycin (100  $\mu\text{g ml}^{-1}$ ), and cultured for 6 h. Transduced bone marrow cells ( $1 \times 10^5$  or  $5 \times 10^5$ ) were then i.v. injected into each of the irradiated female recipients to establish short-term and long-term bone marrow chimaeras, respectively.

In short-term studies, spleens were removed 12 d after transplantation to extract total RNA and genomic DNA. To monitor long-term chimaeras, two or three capillary tubes of blood were collected every 4-6 weeks, from which genomic DNA, total RNA and haemoglobin were extracted. To examine vector function reliably in long-term animals, erythroid cell populations were purified from spleen. Single-cell suspensions were incubated with rat anti-mouse TER-119 monoclonal antibody (PharMingen). Sheep anti-Rat IgG dynabeads (M-450, Dynal Inc.) were added to the antibody-coated spleen cells and purified as recommended by the manufacturer. Vector copy number, integration pattern and chimaerism were determined by Southern blot analysis. The fraction of donor DNA relative to recipient was determined by stripping and reprobing the blot with a [ $^{32}\text{P}$ ] dCTP-labelled probe specific for the Y chromosome and normalizing to an endogenous mouse band. Radioactive bands were quantitated by phosphorimager analysis. Sera from five randomly selected long-term bone marrow chimaeras (30 weeks after transplan-

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tation) tested negative for HIV-1 gag by RT-PCR using the Amplicor HIV-1 monitor kit (Roche).

Vector copy number and human  $\beta$ -globin RNA transcripts were measured during a 24-week period in mice transplanted with RNS1 (n=8) or TNS9 (n=10) transduced bone marrow. a, Vector copy number was assessed by southern blot analysis of genomic DNA isolated from peripheral blood at weeks 6, 10, 16 and 24. The average vector copy number in peripheral blood cells, measured periodically for 24 weeks (FIG. 4), showed highly efficient gene transfer with both vectors (1.8 $\pm$ 0.6 and 0.8 $\pm$ 0.6 average vector copies per cell for  $\beta$ -globin transcript levels in the 10-20% range during the same time period. To assess transcriptional activity per vector copy, steady-state RNA transcripts and vector copy number were quantified in pooled CFU-S<sub>12</sub> and in erythroid TER-119+ spleen cells. Twelve days after transplantation, human  $\beta$ -globin expression per endogenous allele, (FIG. 5a). Twenty weeks later these values were 0.5 $\pm$ 0.1% (significantly lower than on day 12, P=0.02) and 15.8 $\pm$ 0.9% respectively (FIG. 5b). These findings established that the larger LCR fragments increased globin expression in vivo and, furthermore, suggested that TNS9 is more resistant to transcriptional silencing than is RNS1.

The levels of TNS9-encoded human  $\beta$ -globin could be produced. Haemoglobin tetramers incorporating vector-encoded human  $\beta^4$  and endogenous murine  $\alpha$ -globin (designated Hbb<sup>hu</sup>) were quantitated in peripheral blood red cell lysates after cellulose acetate gel fractionation. Hbb<sup>hu</sup> levels accounting for up to 13% of total haemoglobin were found 24 weeks after transplantation (FIG. 3e, Table 1 in Supplementary Information). In the same assays, transgenic mice bearing one copy of a 230-kb yeast artificial chromosome (YAC) encompassing the entire human  $\beta$ -globin like gene cluster<sup>20</sup> showed 14% of their total haemoglobin incorporating human  $\beta^4$ . No haemoglobin tetramers containing human  $\beta^4$  were measurable in any of the mice bearing RNS1 (table 1 in Supplementary Information). The proportion of mature peripheral blood red cells expressing human  $\beta^4$  was elevated in most TNS9 bone marrow chimaeras, as shown by dual staining of human  $\beta^4$  and TER-119. In contrast, chimaeras engrafted with RNS1-transduced bone marrow showed highly variable fractions of weakly staining  $\beta^4$ -positive erythrocytes. Normalized to the fraction of circulating  $\beta^4$ -positive mature red cells, the levels of haemoglobin containing lentivirus-encoded  $\beta^4$  were on average 64% of those obtained in the YAC transgenic mice.

## EXAMPLE 5

To ascertain that true HSCs were transduced, we carried out secondary transplants using marrow from primary recipients collected 24 weeks after transplantation. The TNS9 and RNS1 vectors were readily detected in all secondary recipients 13 weeks after transplantation. Human  $\beta$ -globin expression was maintained in all recipients of TNS9-transduced marrow. The successful transduction of HSCs was confirmed by integration site analyses. Southern blot analysis was performed on genomic DNA isolated from bone marrow, spleen and thymus of secondary bone marrow transplant recipients collected 13 weeks after transplant (one representative RNS1, and two representative TNS9 secondary transplant recipients are shown). Two endogenous bands are found in the genomic DNA of C57BL/6 (B6) mice.

## EXAMPLE 6

In view of the high levels of expression, we tested the extent to which the TNS9 vector could correct the phenotype

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of thalassaemic cells using  $\beta^0$ -thalassaemic heterozygote mice that lack a copy of their b1 and b2  $\beta$ -globin genes (Hbb <sup>$\beta^3/+$</sup> )<sup>21</sup>. These heterozygotes have a clinical phenotype similar to human thalassaemia intermedia and exhibit chronic anaemia (haematocrit 28-30%, haemoglobin 8-9 g dL<sup>-1</sup>) and anomalies in red cell size (anisocytosis) and shape (poikilocytosis). Fifteen weeks after transplantation with unselected TNS9-transduced Hbb <sup>$\beta^3/+$</sup>  bone marrow, the haematocrit level, red blood cell count, reticulocyte count and haemoglobin level were markedly improved in five out of five recipient mice (FIG. 6). Anisocytosis and poikilocytosis were markedly reduced in the peripheral blood smears of chimaeras bearing the TNS9 vector. Control mice transplanted with Hbb <sup>$\beta^3/+$</sup>  bone marrow cells transduced with a vector encoding enhanced green fluorescent protein (eGFP) all remained severely anaemic (n=5, FIG. 6) and maintained their abnormal red cell morphology. These results establish that levels of circulating haemoglobin obtained with TNS9 were indeed therapeutically relevant.

The combined effect of the high efficiency of gene transfer and the absence of vector rearrangements afforded by the recombinant lentivirus carrying the  $\beta$ -globin gene and LCR configuration adopted in TNS9 yielded levels of human  $\beta^4$  expression in the therapeutic range. The higher expression obtained with TNS9 compared with RNS1 was associated with a higher fraction of permissive integration sites in MEL cells and a higher fraction of human  $\beta^4$ -containing red blood cells in bone marrow chimaeras. RNS1, which carries a weaker enhancer, silenced over time whereas TNS9 retained undiminished transcriptional activity over the same time period and in secondary transplant recipients.

Higher levels of murine  $\alpha_2$ : human  $\beta^4$  tetramers were obtained in peripheral blood samples from recipients of TNS9-transduced Hbb <sup>$\beta^3/+$</sup>  bone marrow (21 $\pm$ 3% of total haemoglobin, n=5, than with Hbb <sup>$\beta^3/+$</sup>  bone marrow (6 $\pm$ 4%, n=10). The two groups showed comparable peripheral blood vector copy numbers and levels of human  $\beta$ -globin RNA (0.8 $\pm$ 0.2 compared with 0.8 $\pm$ 0.6, and 16.8 $\pm$ 6% compared with 10.8 $\pm$ 7%, respectively). This observation is consistent with a competitive advantage of murine  $\beta$ -globin over human  $\beta$ -globin in associating with murine  $\alpha$ -globin<sup>22</sup>. In thalassaemic patients, added human  $\beta$ -chain synthesis would improve the  $\alpha$ : $\beta$  chain imbalance and thus increase red cell survival and ameliorate the ineffective erythropoiesis in these patients. In patients with sickle cell disease, transduced  $\beta^4$  chains are expected to have an advantage over the  $\beta^S$  chains produced by both endogenous genes in competing for the available  $\alpha$ -chains<sup>23</sup>. Given that patients with S/ $\beta$ -thalassaemia whose HbA represents 10-30% of their total haemoglobin are very mildly affected<sup>1/24</sup>, the clinical benefit of such an intervention would be highly significant.

## EXAMPLE 7

To investigate long-term expression of the transduced human  $\beta$ -globin genes and its therapeutic efficacy, we generated bone marrow chimeras engrafted with TNS9-transduced Hbb <sup>$\beta^3/+$</sup>  bone marrow cells (n=5) and studied them over a 40-week period.

Donor bone marrow was flushed from the tumors of 8- to 16-week old male c57/BL6 or Hbb <sup>$\beta^3/+$</sup>  mice<sup>23</sup> obtain from Jackson Laboratories (Bar Harbor, Me.) that had been injected intravenously (IV) 6 days earlier with 5-fluorouracil (5-FU) 150 mg/kg body weight obtained from Pharmacia (Piscataway, N.J.). Bone marrow cells were resuspended in X-VIVO-15 serum-free medium and supplemented with 10 ng/mL interleukin-1  $\alpha$  (IL-1 $\alpha$ ) 100 U/mL IL-3, 150 U/mL

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IL-6, 10 ng/mL Kit ligand obtained from Genzyme (Cambridge, Mass.), 0.5 mM  $\beta$ -mercaptoethanol obtained from Sigma (St. Louis, Mo.), 200-mM L-glutamine, 100 IU/mL penicillin, and 100  $\mu$ g/mL streptomycin. Bone marrow cells were then pelleted and resuspended in serum-free medium containing concentrated lentiviral supernatant and supplemented with 8 mg/mL polybrene (Sigma), 200 mM L-glutamine, 100 U/mL penicillin, 100  $\mu$ g/mL streptomycin and cytokines as above, and cultured for 8 hours. Transduced bone marrow cells ( $5 \times 10^5$ ) were then injected IV into each of the irradiated female recipients to establish bone marrow chimeras. Recipients mice (11- to 14-week-old C57/BL6 or Hbb $^{th3/+}$  mice) were irradiated with 10.5 Gy (Split dose  $2 \times 5.25$  Gy) on the day of transplantation.

Age-matched chimeras engrafted with eGFP-transduced Hbb $^{th3/+}$  (n=5) and Hbb $^{+/+}$  (n=5) bone marrow cells served as controls. Vector copy number was monitored in peripheral blood by quantitative Southern blot analysis, and found to remain stable, between 0.5 and 1.0 copy/cell on average (data not shown). Protein expression was assessed by quantitative hemoglobin analysis, to measure the proportion of hemoglobin tetramers that incorporate human  $\beta^4$  (Hbb $^{hu}$ , mu  $\alpha_2$ : hu $\beta^4_2$ ) or murine  $\beta$ -globin (Hbb $^{mu}$ , mu $\alpha_2$ :mu $\beta^4_2$ ), and immunofluorescence, to determine the fraction of mature RBCs that contain human  $\beta^4$  protein. Transgenic mice bearing one copy of a 230-kb yeast artificial chromosome encompassing the entire human  $\beta$ -globin-like gene cluster<sup>28</sup> served as reference, showing 14% of their total hemoglobin incorporating human  $\beta^4$  and 100%  $\beta^4$ +RBCs<sup>19,28</sup>. Hbb $^{hu}$  accounted for 19% to 22% of the total hemoglobin in TNS9 chimeras. These levels remained stable up to 40 weeks after transplantation. Over this same time period, the proportion of mature peripheral RBCs expressing human  $\beta^4$  also remained elevated and stable (about 70% to 80%), as shown by dual staining of human  $\beta^4$  and TER-119.

## EXAMPLE 8

## Long-Term Amelioration of Anemia

The stability of TNS9-encoded  $\beta^4$  expression detected in peripheral blood suggested that long-term hematologic and systemic therapeutic benefits could be obtained. To investigate whether Hbb $^{hu}$  production would suffice to treat the anemia, we closely monitored hemoglobin parameters over 40 weeks. The marked increase in hemoglobin concentration, RBC counts, and hematocrit was sustained throughout this time period. Control mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  bone marrow cells remained severely anemic, indicating that the transplantation procedure itself did not alter the anemic state. The reticulocyte counts decreased to 5% to 8% in TNS9 treated-chimeras, compared to 19% to 21% in control eGFP-treated Hbb $^{th3/+}$  chimeras and age-matched Hbb $^{th3/+}$  mice, suggesting an increase in RBC life span and a decrease in erythropoietic activity.

## EXAMPLE 9

To determine the impact of sustained human  $\beta$ -globin gene expression on hematopoiesis, we studied the degree of splenomegaly (enlargement of the spleen) and EMH in 1-year-old chimeras and age-matched control mice. Spleen weights measured in Tns9-treated Hbb $^{th3/+}$  chimeras were indistinguishable from recipients of eGFP-transduced normal bone marrow, as were the total number of cells per spleen. In contrast, mice engrafted with eGFP-transduced Hbb $^{th3/+}$  bone marrow cells showed spleen weights and total cell numbers that were about 3-fold greater. The correction of spleen

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weight in TNS9 bone marrow chimeras corresponded to a concomitant normalization in total hematopoietic progenitor cell content. Spleen CFU-Es, BFUEs, and CFUs-GM were reduced to levels measured in recipients of eGFP-transduced Hbb $^{th3/+}$  bone marrow, whereas they remained elevated in control chimeras engrafted with eGFP-transduced Hbb $^{th3/+}$  bone marrow cells and in age-matched Hbb $^{th3/+}$  mice, as previously observed in another murine model of  $\beta$ -thalassemia.<sup>29</sup>

The regression of EMH was corroborated by morphologic examination of spleen and liver in long-term chimeras and age-match controls. Histopathology of spleens of mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  marrow was virtually identical to that of spleen from control Hbb $^{th3/+}$  mice. Specifically, the red pulp was significantly expanded, accounting for 80% to 90% of the cross-sectional area, and densely occupied by nucleated erythroid precursors. The white pulp, based on cross-sectional area, was relatively decreased and the marginal zones were obscured by the large number of nucleated RBCs, reflecting major expansion of the red pulp and erythroid precursors. In TNS9-treated chimeras, the amount of red pulp was considerably decreased, accounting for only about 50% to 60% of the cross-sectional area. In addition, the number of nucleated erythroid precursors in the red pulp was decreased. Other immature hematopoietic cells were present in the red pulp, but much less frequently than in the spleens of control Hbb $^{th3/+}$  thalassemic mice. The livers from TNS9-treated chimeras were similar to those of the normal control mice in that no EMH was detected. In contrast, livers from mice engrafted with eGFP-transduced Hbb $^{th3/+}$  bone marrow cells showed several small foci of intrasinusoidal EMH.

## EXAMPLE 10

Toxic iron accumulation in the organs of thalassemic patients is a consequence of RBC destruction and increased gastrointestinal iron uptake. To determine whether sustained expression from the TNS9 vector reduced iron overload, we studied tissue sections of liver and heart, stained using Gomori iron stain. No iron deposition was seen in the livers of normal Hbb $^{+/+}$  control mice, whereas Hbb $^{th3/+}$  mice showed variable amounts of iron, including some large aggregates. TNS9-transduced treated chimeras demonstrated low to undetectable levels of iron in the livers, whereas iron was readily detected in the livers of all mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  bone marrow cells. No iron accumulation was found in the heart of treated or control mice, as previously observed in another murine model of  $\beta$ -thalassemia,<sup>30</sup> in contrast to what is found in the human disease.<sup>1-3</sup>

## EXAMPLE 11

To assess to efficacy of in vivo selection for cells transduced with globin and DHFR-encoding vectors in accordance with the invention, using antifolates the following alternative protocols are used. In protocol 1, the recipient mice are treated daily for 5 days with MTX (25 mg/Kg) and NBMPR-P (20 mg/Kg), starting 6 weeks after administration of transduced bone marrow cells. In protocol 2, the recipient mice are treated daily for 5 days with TMTX (40 mg/Kg) and NBMPR-P (20 mg/Kg), starting 6 weeks after administration of transduced bone marrow cells. In protocol 3, the recipient mice, conditioned with busulphan rather than with gamma-irradiation, are treated daily for 5 days with TMTX (40 mg/Kg) and NBMPR-P (20 mg/Kg), starting 4 weeks after administration of transduced bone marrow cells. (TMTX

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(Neutrexin; U.S. Bioscience); >MTX (Methotrexate LPP Sodium; Immunex); NBMPR-P (Nitrobenzylthioinosine 5'-monophosphate disodium salt; Alberta nucleoside therapeutics). Protocol 3 is in principle the most attractive protocol as the recipients are not irradiated and furthermore not treated with a "myeloablative conditioning regimen". They are treated with a relatively milder conditioning regimen consisting of a "non-myeloablative" dose of busulphan. It is hoped that, in combination with "in vivo selection" mediated by DHFR/TMTX, the recipients could be satisfactorily engrafted without receiving a harsh pre-transplant treatment. This would be the way to go for treating subjects with severe hemoglobinopathies.

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3. The vector of claim 2, further comprising a mouse PGK promoter to control the expression of the dihydrofolate reductase.

4. The vector of claim 3, wherein the dihydrofolate reductase is a human dihydrofolate reductase.

5. The vector of claim 4, wherein the human dihydrofolate reductase is a mutant dihydrofolate reductase having increased resistance to antifolates as compared to wild-type human dihydrofolate reductase and differing in amino acid sequence from wild-type human dihydrofolate reductase.

6. The vector of claim 5, wherein the mutant dihydrofolate reductase comprises a mutation at an amino acid correspond-

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SEQUENCE LISTING

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<211> LENGTH: 27

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<400> SEQUENCE: 2

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27

<210> SEQ ID NO 3

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<212> TYPE: DNA

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22

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<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: mouse

<400> SEQUENCE: 4

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23

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What is claimed is:

1. A recombinant vector comprising a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human  $\beta$ -globin locus control region (LCR), the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR, said vector providing expression of the globin in a mammal *in vivo*.

2. The vector of claim 1, further comprising a nucleic acid encoding a dihydrofolate reductase.

55 ing to amino acid 22 of the wild-type sequence and a mutation at an amino acid corresponding to amino acid 31 of the wild type sequence.

7. The vector of claim 2, wherein the dihydrofolate reductase is a human dihydrofolate reductase.

60 8. The vector of claim 7, wherein the human dihydrofolate reductase is a mutant dihydrofolate reductase having increased resistance to antifolates as compared to wild-type human dihydrofolate reductase and differing in amino acid sequence from wild-type human dihydrofolate reductase.

65 9. The vector of claim 8, wherein the mutant dihydrofolate reductase comprises a mutation at an amino acid correspond-

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ing to amino acid 22 of the wild-type sequence and a mutation at an amino acid corresponding to amino acid 31 of the wild type sequence.

**10.** The vector of claim **1**, wherein the functional globin is human  $\beta$ -globin.

**11.** The vector of claim **10**, further comprising a nucleic acid encoding a dihydrofolate reductase.

**12.** The vector of claim **11**, further comprising a mouse PGK promoter to control the expression of the dihydrofolate reductase.

**13.** The vector of claim **12**, wherein the dihydrofolate reductase is a human dihydrofolate reductase.

**14.** The vector of claim **13**, wherein the human dihydrofolate reductase is a mutant dihydrofolate reductase having increased resistance to antifolates as compared to wild-type human dihydrofolate reductase and differing in amino acid sequence from wild-type human dihydrofolate reductase.

**15.** The vector of claim **14**, wherein the mutant dihydrofolate reductase comprises a mutation at an amino acid corresponding to amino acid 22 of the wild-type sequence and a mutation at an amino acid corresponding to amino acid 31 of the wild type sequence.

**16.** The vector of claim **11**, wherein the dihydrofolate reductase is a human dihydrofolate reductase.

**17.** The vector of claim **16**, wherein the human dihydrofolate reductase is a mutant dihydrofolate reductase having increased resistance to antifolates as compared to wild-type human dihydrofolate reductase and differing in amino acid sequence from wild-type human dihydrofolate reductase.

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**18.** The vector of claim **17**, wherein the mutant dihydrofolate reductase comprises a mutation at an amino acid corresponding to amino acid 22 of the wild-type sequence and a mutation at an amino acid corresponding to amino acid 31 of the wild type sequence.

**19.** The vector of claim **1**, wherein the functional globin is a  $\beta$ -globin.

**20.** The vector of claim **1**, wherein the functional globin is a  $\gamma$ -globin.

**21.** The vector of claim **1**, wherein the functional globin is an  $\alpha$ -globin.

**22.** The vector of claim **1**, wherein the vector is a lentiviral vector.

**23.** A recombinant vector comprising a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three nucleotide fragments obtainable from a human  $\beta$ -globin LCR, the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII, HS3-

spanning nucleotide fragment of said LCR, and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR, wherein the HS3-spanning nucleotide fragment and the HS4-spanning nucleotide fragment are adjacent to each other and the vector further comprises 2 GATA-1 binding sites at the junction between the HS3-spanning and HS4-spanning nucleotide fragments, said vector providing expression of the globin in a mammal *in vivo*.

**24.** The vector of claim **23**, wherein the vector is pTNS9.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,541,179 B2  
APPLICATION NO. : 10/188221  
DATED : June 2, 2009  
INVENTOR(S) : Sadelain et al.

Page 1 of 1

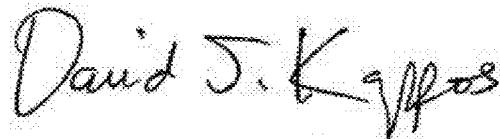
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)  
by 682 days.

Signed and Sealed this  
Twenty-third Day of August, 2011



David J. Kappos  
*Director of the United States Patent and Trademark Office*

# EXHIBIT B



US008058061B2

(12) **United States Patent**  
**Sadelain et al.**

(10) **Patent No.:** US 8,058,061 B2  
(45) **Date of Patent:** Nov. 15, 2011

(54) **VECTOR ENCODING HUMAN GLOBIN GENE AND USE THEREOF IN TREATMENT OF HEMOGLOBINOPATHIES**

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(73) Assignee: **Memorial Sloan-Kettering Cancer Center**, New York City, NY (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 147 days.

(21) Appl. No.: **12/433,412**

(22) Filed: **Apr. 30, 2009**

(65) **Prior Publication Data**

US 2009/0274671 A1 Nov. 5, 2009

**Related U.S. Application Data**

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(60) Provisional application No. 60/301,861, filed on Jun. 29, 2001, provisional application No. 60/302,852, filed on Jul. 2, 2001.

(51) **Int. Cl.**

**C12N 5/00** (2006.01)  
**C12N 15/00** (2006.01)  
**C12N 15/67** (2006.01)  
**C12N 15/11** (2006.01)

(52) **U.S. Cl.** ..... **435/325; 435/326; 435/320.1; 435/69.1; 536/24.1; 536/24.2**

(58) **Field of Classification Search** ..... None  
See application file for complete search history.

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**Primary Examiner — Maria Marvich**

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(57) **ABSTRACT**

Recombinant lentiviral vectors having a region encoding a functional β-globin gene; and large portions of the β-globin locus control regions which include DNase I hypersensitive sites HS2, HS3 and HS4 provides expression of β-globin when introduced into a mammal, for example a human, in vivo. Optionally, the vector further includes a region encoding a dihydrofolate reductase. The vector may be used in treatment of hemoglobinopathies, including β-thalassemia and sickle-cell disease. For example, hematopoietic progenitor or stem cells may be transformed ex vivo and then restored to the patient. Selection processes may be used to increase the percentage of transformed cells in the returned population. For example, a selection marker which makes transformed cells more drug resistant than untransformed cells allows selection by treatment of the cells with the corresponding drug.

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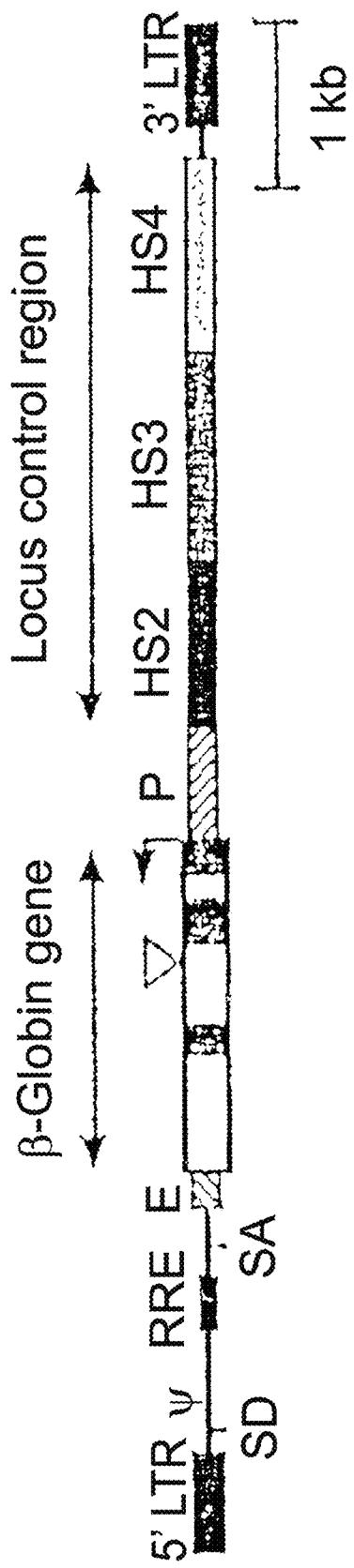


Fig. 1

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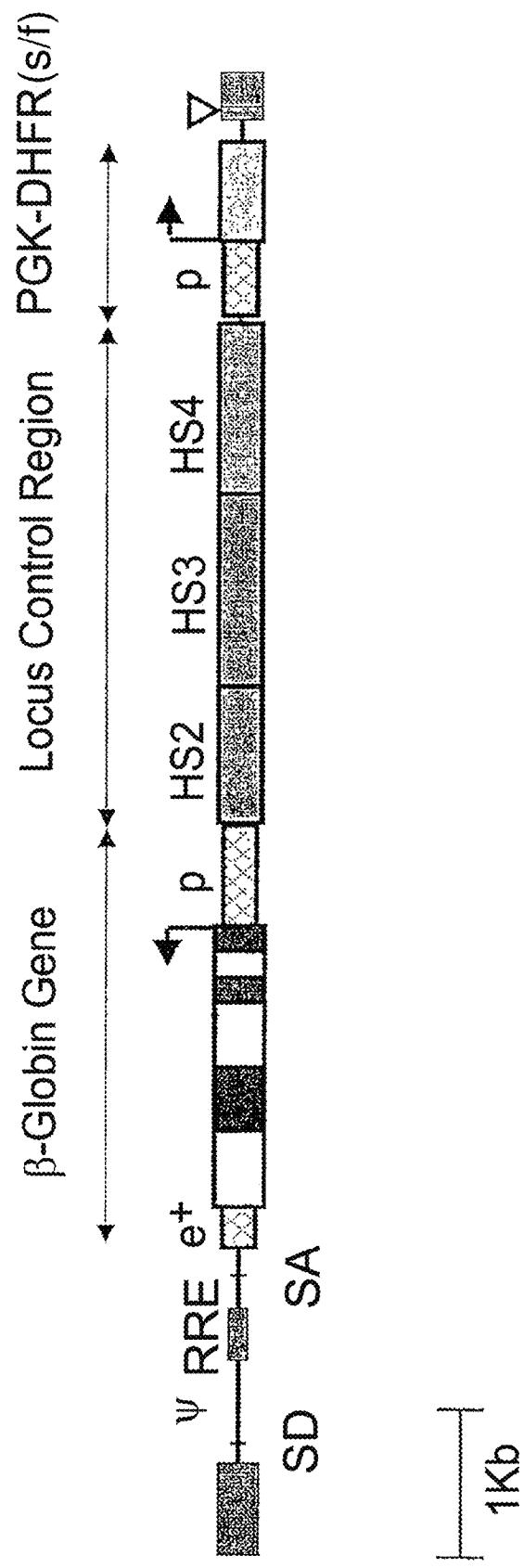
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## Clinical Use of Drug Resistance

### In Vivo Selection of Genetically Modified Stem Cells



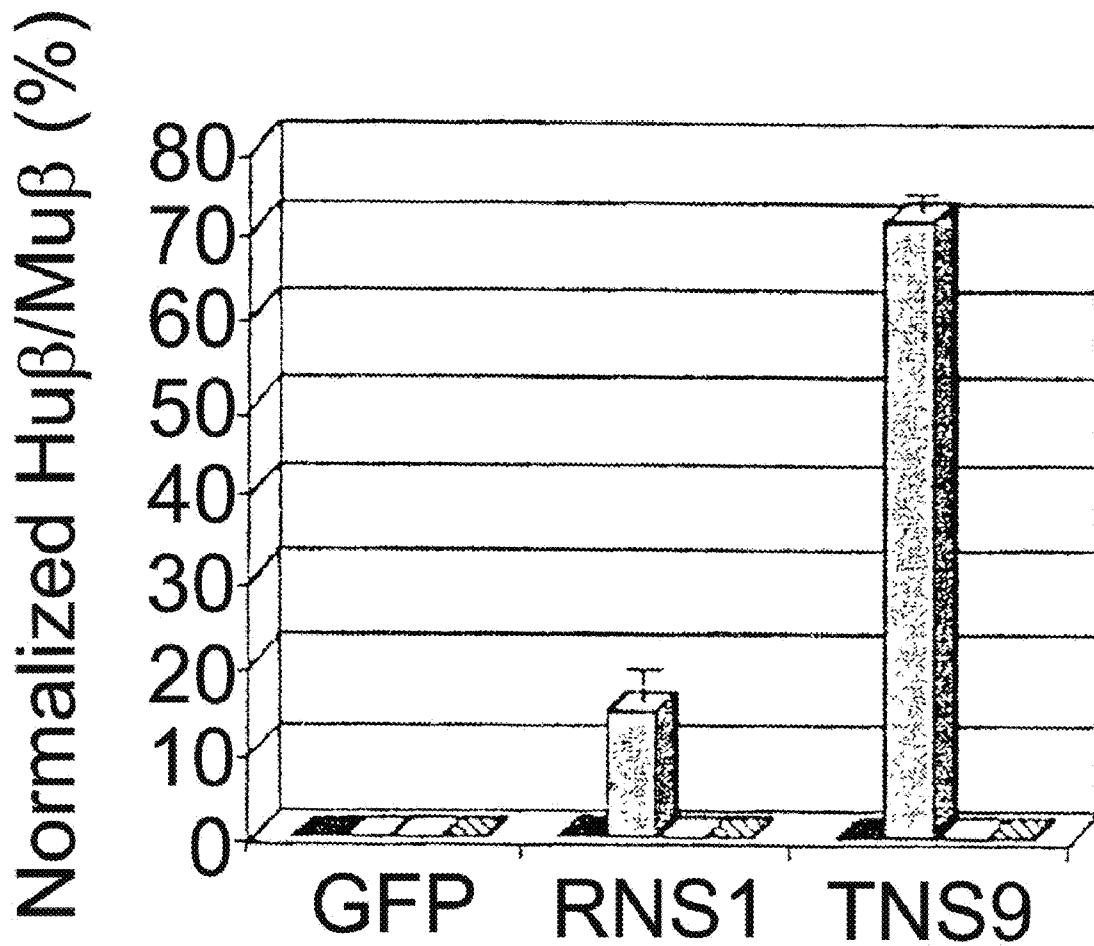
**Fig. 2**

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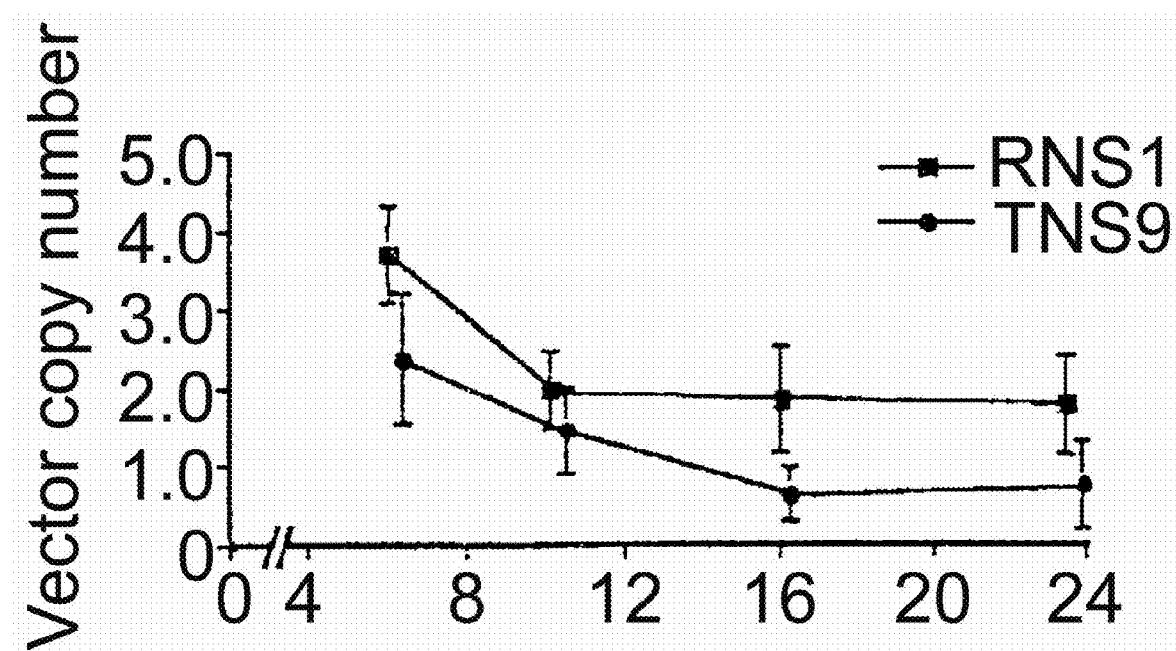
**Fig. 3**

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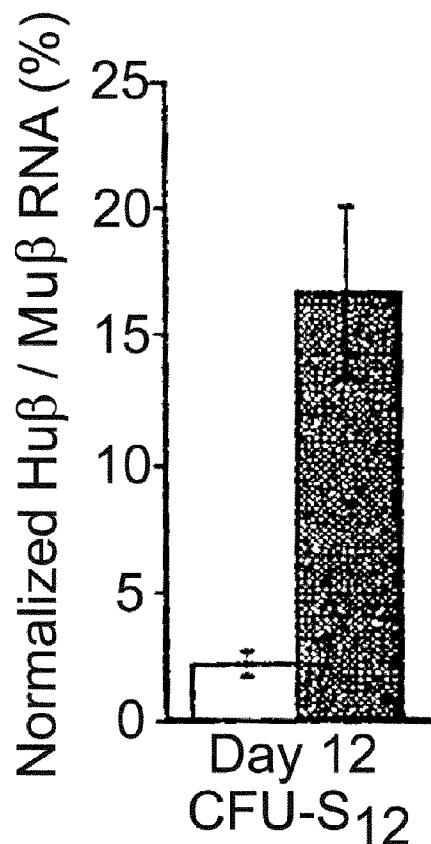
**Fig. 4**

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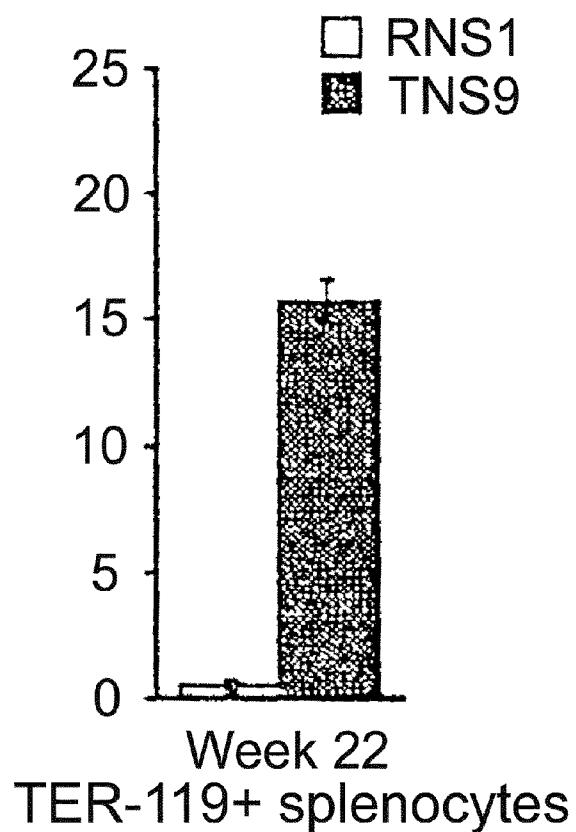
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**Fig. 5A**



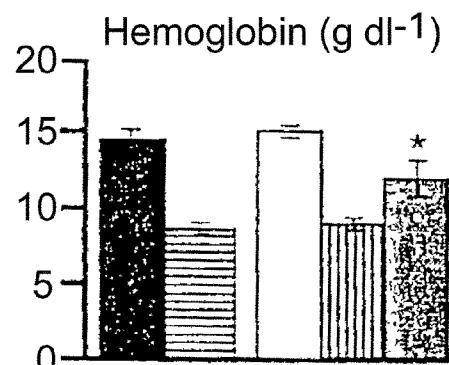
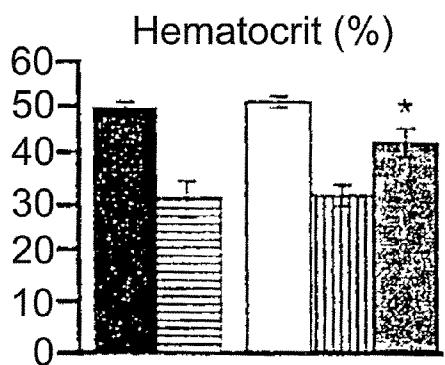
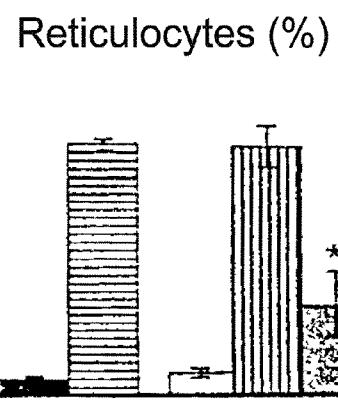
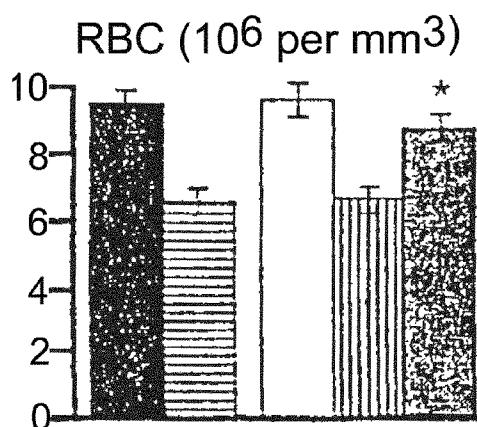
**Fig. 5B**

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Donor mice

- Hbb<sup>+/+</sup>
- ▨ Hbb<sup>th3/+</sup>

Bone marrow chimaeras

- Hbb<sup>+/+/-GFP</sup>
- ▨ Hbb<sup>th3/+-GFP</sup>
- ▨ Hbb<sup>th3/+-TNS9</sup>

**Fig. 6**

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**VECTOR ENCODING HUMAN GLOBIN  
GENE AND USE THEREOF IN TREATMENT  
OF HEMOGLOBINOPATHIES**

**STATEMENT CONCERNING RELATED  
APPLICATIONS**

This application is a divisional application of U.S. Ser. No. 10/188,221, filed Jul. 1, 2002, now U.S. Pat. No. 7,541,179, which claims the benefit of U.S. Provisional Application No. 60/301,861 filed Jun. 29, 2001 and U.S. Provisional Application No. 60/302,852 filed Jul. 2, 2001, each of which is incorporated herein by reference.

**STATEMENT CONCERNING GOVERNMENT  
FUNDING**

The invention disclosed in this application was made with funds provided under NHLBI grant No. HL57612. The United States government has certain rights in the invention.

**BACKGROUND OF THE INVENTION**

This application relates to a vector comprising a mammalian, and particularly a human globin gene and to the use thereof in treatment of hemoglobinopathies, including α- and β-thalassemia and sickle-cell disease.

Current treatment modalities for β-thalassemias consist of either red blood cell transfusion plus iron chelation (which extends survival but is cumbersome, expensive and an imperfect therapy), or allogeneic bone marrow transplant (which carries a lethal risk and is not available to the majority of patients). Thus, there is a substantial need for improved therapeutic approaches. The present invention provides a genetic correction in autologous hematopoietic stem cells, thus using gene therapy to provide a less-risky and more effective long-term treatment.

While gene therapy has been proposed for many years, a significant challenge facing efforts to develop gene therapy vectors is the ability to produce therapeutically useful levels of a desired protein or peptide. The present invention provides a vector which is capable of providing therapeutically meaningful levels of human globin for sustained periods of time. This ability arises from the ability to transmit large genomic regulatory sequences that control expression of the therapeutic gene.

**SUMMARY OF THE INVENTION**

In accordance with the invention, a recombinant lentiviral vector is provided comprising:

- (a) a region comprising a functional globin gene; and
- (b) large portions of the β-globin locus control regions which include large portions of DNase I hypersensitive sites HS2, HS3 and HS4. The regions may be the complete site or some lesser site which provides the same functionality as the specific sequences set forth below. This vector provides expression of β-globin when introduced into a mammal, for example a human, *in vivo*. Optionally, the vector further comprises a region encoding a dihydrofolate reductase.

By incorporation of different globin genes, the vector of the invention may be used in treatment of hemoglobinopathies, including α- and β-thalassemia and sickle-cell disease. For example, hematopoietic progenitor or stem cells may be transformed *ex vivo* and then restored to the patient. Selection processes may be used to increase the percentage of trans-

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formed cells in the returned population. For example, a selection marker which makes transformed cells more drug resistant than un-transformed cells allows selection by treatment of the cells with the corresponding drug. Selection and/or enrichment may also be carried out *in vivo*, for example using methotrexate or similar antifolates to select for cells rendered resistant by the expression from the vector of a dihydrofolate reductase (DHFR).

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 shows the genomic structure of a recombinant onco-retroviral vector in accordance with the invention.

FIG. 2 shows the genomic structure of recombinant onco-retroviral vector within the scope of the invention.

FIG. 3 shows experimental results demonstrating increased mean (β-globin expression in transduced MEL cells.

FIG. 4 shows the average vector copy number in peripheral blood cells, measured periodically for 24 weeks, which confirms highly efficient gene transfer in cells transduced with the vector of the invention.

FIGS. 5A and B show human (β-globin expression per endogenous allele 12 days and 22 weeks after introduction of cells transduced with the vector of the invention.

FIG. 6 shows haematocrit level, red blood cell count, reticulocyte count and haemoglobin level fifteen weeks after transplantation with unselected TNS9-transduced Hbb<sup>th3/+</sup> bone marrow.

**DETAILED DESCRIPTION OF THE INVENTION**

In a first aspect of the present invention, a recombinant lentiviral vector is provided comprising:

- (a) a region comprising a functional globin gene; and
- (b) large portions of the (β-globin locus control regions, which include DNase I hypersensitive sites HS2, HS3 and HS4.

As used in the specification and claims hereof, the term "recombinant lentiviral vector" refers to an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation.

The term "functional globin gene" refers to a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene. The functional globin gene may encode a wild-type globin appropriate for a mammalian individual to be treated, or it may be a mutant form of globin, preferably one which provides for superior properties, for example superior oxygen transport properties. The functional globin gene includes both exons and introns, as well as globin promoters and splice donors/acceptors. Suitably, the globin gene may encode α-globin, β-globin, or γ-globin. β-globin promoters may be used with each of the globin genes.

The recombinant vectors of the invention also include large portions of the locus control region (LCR) which include DNase I hypersensitive sites HS2, HS3 and HS4. In prior studies, smaller nucleotide fragments spanning the core portions of HS2, HS3 and HS4 have been utilized. Sadelain et al. *Proc. Nat'l Acad. Sci. (USA)* 92: 6728-6732 (1995); Lebouich et al., *EMBO J.* 13: 3065-3076 (1994). The term "large portions" refers to portions of the locus control region which encompass larger portions of the hypersensitive sites as opposed to previously tested fragments including only the core elements. The regions may be the complete site or some

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lesser site which provides the same functionality as the specific sequences set forth below. In preferred embodiments of the invention, the large portions of the locus control regions are assembled from multiple fragments, each spanning one of the DNase I hypersensitive sites. In addition, the locus control region has two introduced GATA-1 binding sites at the junction between HS3 and HS4. While not intending to be bound by any specific mechanism, it is believed that the incorporation of these transcription factor binding sites enhances the effectiveness of the vector.

The genomic structure of one embodiment of the vector of the invention (TNS9) is shown in FIG. 1. TNS9 incorporates human β-globin gene (from position -618 to +2484) that includes an extended promoter sequence and a 3'-enhancer element. Optionally, a portion of 3' U3 region of the lentiviral backbone can be deleted for increased safety. In FIG. 1, the exons and introns of the human β-globin gene are represented by filled and open boxes. The locations are indicated for the splice donor (SD), splice acceptor (SA), packaging region ( $\psi$ ), rev-response element (RRE), human β-globin promoter (P) and 3'-β-globin enhancer (E). Thus, in the vector TNS9, a functional β-globin gene, which includes both the exons and introns of the gene and the relevant control sequences from the human β-globin locus. These are combined with the large fragments of the locus control region. The 3.2 kb LCR assembled into dTNS9 consists of an 840 bp HS2 fragment (SnaBI-BstXI), a 1308 bp HS3 fragment (HindIII-BamHI) and a 1069 bp HS4 fragment (BamHI-BanII).

In a further aspect of the invention, the β-globin gene coding sequence can be exchanged and replaced with either the gamma globin gene (for sickle cell disease) or the alpha globin gene (for alpha-thalassemias). In one strategy, a NcoI-Pst I fragment of the β-globin gene is replaced with the corresponding NcoI-HindIII fragment of the gamma globin gene or the NcoI-PstI fragment of the human alpha globin gene. These fragments start at the translational start of each globin gene (spanning the NcoI site) and end past their respective polyadenylation signals. In the second strategy, chimeric genes can be generated by only swapping the coding sequence of each one of the three exons of these genes. Thus, for the gamma globin gene, the result is a vector that comprises the beta globin promoter, the beta globin 5' untranslated region, the gamma exon 1 coding region, the gamma intron 1 the gamma exon 2, the beta intron 2, the gamma exon 3, and the beta 3' untranslated region. Thus all the elements of the TNS9 vector remain in place (promoter, enhancers, 5' and 3' untranslated regions, the LCR elements, the 2 additional GATA-1 binding sites and the introns of the beta globin gene (at least intron 2, which is most important). In a third strategy, the codon usage within exon 3 of the gamma globin gene can be modified so that its sequence will resemble as much as possible that of the beta globin gene. The reason for testing this is that the beta globin gene is always the best expressed.

Additional elements may be included in the vectors of the invention to facilitate utilization of the vector in therapy. For example, the vector may include selectable markers, to confirm the expression of the vector or to provide a basis for selection of transformed cells over untransformed cells, or control markers which allow targeted disruption of transformed cells, and thus the selective removal of such cells should termination of therapy become necessary.

In a further specific embodiment, the vector of the invention includes the mouse PGK promoter and human dihydrofolate reductase (DHFR) cDNA as a transcriptional unit. Mutant forms of DHFR which increase the capacity of the DHFR to confer resistance to drugs such as methotrexate are suitably used. For example, single and double mutants of

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DHFR with mutations at amino acids 22 and 31 as described in commonly assigned PCT Publication No. WO 97/33988, which is incorporated herein by reference, may be advantageously utilized.

FIG. 2 shows the genomic structure of specific vector within the scope of the invention. The vector includes a deleted LTR, from -456 to -9 of HIV LTR and the PGK promoter (530 bp) from the murine phosphoglycerate kinase 1 gene. It also includes a DHFR-encoding region encoding human DHFR with s/f mutation at amino acid 22. The locus control region and the β-globin region are the same as in TSN9. This vector is designated dTNS9-PD. This incorporation of DHFR into this vector provides transformed cells with a methotrexate-resistant phenotype. As a result, methotrexate, and other antifolates can be used, both *in vitro* and *in vivo* as a selection tool to enhance levels of the functional hemoglobin. When hematopoietic stem cells were transformed using dTNS9-PD and reintroduced to mice that were then treated with NMBPR-P (0.5 mg/dose) and TMTX (0.5 mg dose) for five days, observed levels of expressed human β-globin were much higher in mice transduced with dTNS9-PD vectors after treatment with TMTX and NMBPR-P for selection of transduced cells.

The vectors of the invention are used in therapy for treatment of individuals suffering from hemoglobinopathies. In one embodiment of the invention, hematopoietic progenitor or stem cells are transformed *ex vivo* and then restored to the patient. As used in the specification and claims hereof, the term "hematopoietic progenitors and stem cells" encompasses hematopoietic cells and non-hematopoietic stem cells, e.g., embryonic stem cells, hematopoietic stem cell precursors, or any of the latter generated by nuclear transfer from a somatic cell. It is known in the art that efficient gene transfer into human embryonic stem cells can be achieved using lentiviral vectors.

Selection processes may be used to increase the percentage of transformed cells in the returned population. For example, a selection marker which makes transformed cells more drug resistant than un-transformed cells allows selection by treatment of the cells with the corresponding drug. When DHFR is used as a selection marker, it can be used for enrichment of transduced cells *in vitro*, or for *in vivo* selection to maintain the effectiveness of the vector.

The invention will now be further described with reference to the following non-limiting examples.

## EXAMPLE 1

To produce vector TNS9, the human β-globin gene was subcloned from Mβ6L (Sadelain et al. *Proc. Natl Acad. Sci. (USA)* 92: 6728-6732 (1995)) into lentiviral vector pHR'LacZ (Zuffery et al., *Nature* 15: 871-875 (1997)) replacing the CMV-LacZ sequence. pHR'eGFP was constructed by replacing LacZ with the eGFP sequence (Clontech). Viral stocks were generated by triple transfection of the recombinant vectors pCMVΔR8.9 (Zuffrey et al.) and pMD.G in 293T cells as previously described in Dull, et al., *J. Virol.* 72: 8463-8471 (1998). The pseudotyped virions were concentrated by ultracentrifugation resuspended and titrated as described in Gallardo et al., *Blood* 90: 952-957 (1997). For comparison, RSN1 was used which has a similar structure, except that the LCR contains only the core portion of HS2, HS3 and HS4. Northern blot analysis showed full length RNA transcripts, indicating that the recombinant lentiviral genomes are stable. Southern blot analysis on genomic DNA from transduced cells, digested once in each long terminal

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repeat (LTR) results in a single band corresponding to the expected size for the vector, indicating that the proviral structure is not rearranged.

## EXAMPLE 2

To investigate the tissue specificity, stage specificity and expression level of the vector-encoded human  $\beta$ -globin gene, we transduced RNS1 and TNS9 into MEL cells, lymphoid Jurkat cells and myeloid HL-60 cells. Cell-free viral supernatant was used to infect C88 MEL cells in the presence of polybrene ( $8 \mu\text{g ml}^{-1}$ ). Transduced MEL cells were subcloned by limiting dilution, and screened by PCR for transduction<sup>30</sup> using primers that anneal in the human  $\beta$ -globin promoter sequence (OPS, 5'-GTCTAACGTGATGACAGC-  
CGTACCTG-3'; SEQ ID NO:1) and in HS2 (C2A,  
5'-TCAGCCTAGAGT GATGACTCC TATCTG-3'; SEQ ID NO:2). Vector copy number and integration site analysis was determined by Southern blot analysis<sup>9</sup>. Transduced MEL cells were induced to maturation by 5-day culture in 5 mM N,N'-hexamethylene bisacetamide (HMBA, Sigma).

To induce ( $\beta$ -globin transcription, transduced MEL cell pools were differentiated using hexamethylene bisacetamide (HMBA). Human ( $\beta$ -globin ( $\beta^4$ ) and mouse ( $\beta$ -globin transcripts were measured by quantitative primer extension. After normalization to vector copy number and to endogenous  $\beta$ -globin expression per allele, human ( $\beta$ -globin levels were  $14.2 \pm 4.7\%$  for RNS1 and  $71.3 \pm 2.3\%$  for TNS9 in pooled MEL cells (FIG. 2a). MEL, Jurkat and HL-60 cells were transduced with RNS1, TNS9 or control GFP recombinant lentivirus. Human  $\beta$ -globin RNA expression in HMBA induced MEL cells (grey bars) was measured by quantitative primer extension and normalized to mouse  $\beta$ -globin RNA expression per locus. Expression was then normalized to the vector copy number determined by Southern blot. No human  $\beta$ -globin RNA expression was detected in non-induced MEL (black bars), Jurkat (white bars) or HL-60 cells (hatched bars), indicating that globin expression was erythroid- and differentiation-specific. No human  $\beta$ -globin expression was detected in non-induced MEL, Jurkat and HL-60 cells (FIG. 3), indicating that human  $\beta$ -globin expression was appropriately regulated in terms of tissue specificity and state of differentiation. We generated a panel of MEL cell clones that carried a single copy of either vector to distinguish whether the increased expression obtained in HMBA-treated Mel cells transduced with TNS9 rather than RNS1 was the result of an increase in  $\beta^4$  expression per cell or of an increase in the fraction of cells expressing human  $\beta$ -globin. Transduced MEL cells were subcloned by limiting dilution immediately after transduction, avoiding any bias towards favourable chromosomal integration sites as produced by drug selection<sup>5</sup>. The proportion of clones expressing human  $\beta$ -globin varied significantly between the two vectors. One out of ten RNS1 positive clones yielded measurable human  $\beta$ -globin transcripts, in contrast to 12 out of 12 for TNS9 also expressed higher levels of human  $\beta$ -globin than did those bearing RNS1 ( $P < 0.01$ , Fisher's exact test). Cells bearing TNS9 also expressed higher levels of human  $\beta$ -globin than did those bearing RNS1 ( $P < 0.01$ , Wilcoxon rank sum test). These findings established that both the level and probability of expression at random integration sites was increased with the TNS9 vector.

## EXAMPLE 3

Quantification of Human  $\beta$ -Globin mRNA

Total RNA was extracted from MEL, Jurkat and HL-60 cells, or mouse spleen and blood using TRIzol. Quantitative

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primer extension assays were done using the Primer Extension System-AMV Reverse Transcriptase kit (Promega) with [ $^{32}\text{P}$ ] dATP end-labelled primers specific for retroviral-derived human  $\beta$ -globin (5'-CAGTAACGGCAGACTTCTC-  
CTC-3'; SEQ ID NO:3) and mouse  $\beta$ -globin (5'-TGAT-  
GTCTGTTCTGGGGTT GTG-3'; SEQ ID NO:4), with predicted extension products of 90 bp and 53 bp, respectively. The probes yield products of identical length for  $\beta^{\text{maj}}$ ,  $\beta^{\text{min}}$ ,  $\beta^s$  and  $\beta^4$ . Primers were annealed to 4  $\mu\text{g}$  of RNA and reactions were run according to manufacturer's protocols. Radioactive bands were quantitated by phosphorimager analysis (Bio-Rad). RNA isolated from A85.68 mice<sup>20</sup> was used as positive control. After correction for primer labelling, the human to mouse RNA signal was  $29 \pm 1\%$  per gene copy in repeated experiments ( $n > 8$ ), in agreement with previous findings based on RT-PCR<sup>20</sup>. Values measured in bone marrow chimaeras that were obtained in separate runs were standardized to the value obtained in the A85.68 RNA sample. In FIGS. 2 and 3c, d, human  $\beta$ -globin expression is expressed per vector copy and normalized to the endogenous transcripts (accounting for two endogenous alleles). In FIG. 3b, human transcripts are reported as the fraction of total  $\beta$ -globin RNA ( $\text{Hu}\beta/\text{Hu}\beta + \text{Mu}\beta$ ) to reflect absolute contribution of vector-encoded transcripts.

## EXAMPLE 4

To investigate the function of the vectors in vivo, we transduced and transplanted murine bone marrow cells without any selection in syngeneic, lethally irradiated recipient mice. Donor bone marrow was flushed from the femurs of 8- to 16-week-old male C57BL/6 or  $\text{Hbb}^{\text{th3/+}}\text{mice}$  (Jackson Laboratories) that had been injected intravenously (i.v.) 6 days earlier with 5-flourouracil (5-FU, Pharmacia; 150 mg  $\text{kg}^{-1}$  body weight). Bone marrow cells were resuspended in serum-free medium, and supplemented with IL-1 $\alpha$  (10 ng  $\text{ml}^{-1}$ ), IL-3 (100 U  $\text{ml}^{-1}$ ), IL-6 (150 U  $\text{ml}^{-1}$ ), Kit ligand (10 ng  $\text{ml}^{-1}$  (Genzyme),  $\beta$ -mercaptoethanol (0.5 mM; Sigma), L-glutamine (200 mM), penicillin (100 IU  $\text{ml}^{-1}$ ) and streptomycin (100  $\mu\text{g ml}^{-1}$ ), and cultured for 18 h. Recipient mice (11- to 14-week-old C57/BL6 or  $\text{Hbb}^{\text{th3/+}}$  mice) were irradiated with 10.5 Gy (split dose  $2 \times 5.25$  Gy) on the day of transplantation. Bone marrow cells were pelleted and resuspended in serum-free medium containing concentrated lentiviral supernatant, and supplemented with polybrene (8  $\mu\text{g ml}^{-1}$ ), L-glutamine (200 mM), penicillin (100 IU  $\text{ml}^{-1}$ ) and streptomycin (100  $\mu\text{g ml}^{-1}$ ), and cultured for 6 h. Transduced bone marrow cells ( $1 \times 10^5$  or  $5 \times 10^5$ ) were then i.v. injected into each of the irradiated female recipients to establish short-term and long-term bone marrow chimaeras, respectively.

In short-term studies, spleens were removed 12 d after transplantation to extract total RNA and genomic DNA. To monitor long-term chimaeras, two or three capillary tubes of blood were collected every 4-6 weeks, from which genomic DNA, total RNA and haemoglobin were extracted. To examine vector function reliably in long-term animals, erythroid cell populations were purified from spleen. Single-cell suspensions were incubated with rat anti-mouse TER-119 monoclonal antibody (PharMingen). Sheep anti-Rat IgG dynabeads (M-450, Dynal Inc.) were added to the antibody-coated spleen cells and purified as recommended by the manufacturer. Vector copy number, integration pattern and chimaerism were determined by Southern blot analysis. The fraction of donor DNA relative to recipient was determined by stripping and reprobing the blot with a [ $^{32}\text{P}$ ] dCTP-labelled probe specific for the Y chromosome and normalizing to an endogenous mouse band. Radioactive bands were quantitated by

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phosphorimager analysis. Sera from five randomly selected long-term bone marrow chimaeras (30 weeks after transplantation) tested negative for HIV-1 gag by RT-PCR using the Amplicor HIV-1 monitor kit (Roche).

Vector copy number and human  $\beta$ -globin RNA transcripts were measured during a 24-week period in mice transplanted with RNS1 (n=8) or TNS9 (n=10) transduced bone marrow. a, Vector copy number was assessed by southern blot analysis of genomic DNA isolated from peripheral blood at weeks 6, 10, 16 and 24. The average vector copy number in peripheral blood cells, measured periodically for 24 weeks (FIG. 4), showed highly efficient gene transfer with both vectors ( $1.8 \pm 0.6$  and  $0.8 \pm 0.6$  average vector copies per cell for  $\beta$ -globin transcript levels in the 10-20% range during the same time period. To assess transcriptional activity per vector copy, steady-state RNA transcripts and vector copy number were quantified in pooled CFU-S<sub>12</sub> and in erythroid TER-119+ spleen cells. Twelve days after transplantation, human  $\beta$ -globin expression per endogenous allele, (FIG. 5a). Twenty weeks later these values were  $0.5 \pm 0.1\%$  (significantly lower than on day 12, P=0.02) and  $15.8 \pm 0.9\%$  respectively (FIG. 5b). These findings established that the larger LCR fragments increased globin expression in vivo and, furthermore, suggested that TNS9 is more resistant to transcriptional silencing than is RNS1.

The levels of TNS9-encoded human  $\beta$ -globin could be produced. Haemoglobin tetramers incorporating vector-encoded human  $\beta^4$  and endogenous murine  $\alpha$ -globin (designated Hbb<sup>hu</sup>) were quantitated in peripheral blood red cell lysates after cellulose acetate gel fractionation. Hbb<sup>hu</sup> levels accounting for up to 13% of total haemoglobin were found 24 weeks after transplantation (FIG. 3e, Table 1 in Supplementary Information). In the same assays, transgenic mice bearing one copy of a 230-kb yeast artificial chromosome (YAC) encompassing the entire human  $\beta$ -globin like gene cluster<sup>20</sup> showed 14% of their total haemoglobin incorporating human  $\beta^4$ . No haemoglobin tetramers containing human  $\beta^4$  were measurable in any of the mice bearing RNS1 (table 1 in Supplementary Information). The proportion of mature peripheral blood red cells expressing human  $\beta^4$  was elevated in most TNS9 bone marrow chimaeras, as shown by dual staining of human  $\beta^4$  and TER-119. In contrast, chimaeras engrafted with RNS1-transduced bone marrow showed highly variable fractions of weakly staining  $\beta^4$ -positive erythrocytes. Normalized to the fraction of circulating  $\beta^4$ -positive mature red cells, the levels of haemoglobin containing lentivirus-encoded  $\beta^4$  were on average 64% of those obtained in the YAC transgenic mice.

## EXAMPLE 5

To ascertain that true HSCs were transduced, we carried out secondary transplants using marrow from primary recipients collected 24 weeks after transplantation. The TNS9 and RNS1 vectors were readily detected in all secondary recipients 13 weeks after transplantation. Human  $\beta$ -globin expression was maintained in all recipients of TNS9-transduced marrow. The successful transduction of HSCs was confirmed by integration site analyses. Southern blot analysis was performed on genomic DNA isolated from bone marrow, spleen and thymus of secondary bone marrow transplant recipients collected 13 weeks after transplant (one representative RNS1, and two representative TNS9 secondary transplant recipients are shown). Two endogenous bands are found in the genomic DNA of C57BL/6 (B6) mice.

## EXAMPLE 6

In view of the high levels of expression, we tested the extent to which the TNS9 vector could correct the phenotype

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of thalassaemic cells using  $\beta^0$ -thalassaemic heterozygote mice that lack a copy of their b1 and b2  $\beta$ -globin genes (Hbb<sup>th3/+</sup>)<sup>21</sup>. These heterozygotes have a clinical phenotype similar to human thalassaemia intermedia and exhibit chronic anaemia (haematocrit 28-30%, haemoglobin 8-9 g dl<sup>-1</sup> and anomalies in red cell size (anisocytosis) and shape (poikilocytosis). Fifteen weeks after transplantation with unselected TNS9-transduced Hbb<sup>th3/+</sup> bone marrow, the haematocrit level, red blood cell count, reticulocyte count and haemoglobin level were markedly improved in five out of five recipient mice (FIG. 6). Anisocytosis and poikilocytosis were markedly reduced in the peripheral blood smears of chimaeras bearing the TNS9 vector. Control mice transplanted with Hbb<sup>th3/+</sup> bone marrow cells transduced with a vector encoding enhanced green fluorescent protein (eGFP) all remained severely anaemic (n=5, FIG. 6) and maintained their abnormal red cell morphology. These results establish that levels of circulating haemoglobin obtained with TNS9 were indeed therapeutically relevant.

The combined effect of the high efficiency of gene transfer and the absence of vector rearrangements afforded by the recombinant lentivirus carrying the  $\beta$ -globin gene and LCR configuration adopted in TNS9 yielded levels of human  $\beta^4$  expression in the therapeutic range. The higher expression obtained with TNS9 compared with RNS1 was associated with a higher fraction of permissive integration sites in MEL cells and a higher fraction of human  $\beta^4$ -containing red blood cells in bone marrow chimaeras. RNS1, which carries a weaker enhancer, silenced over time whereas TNS9 retained undiminished transcriptional activity over the same time period and in secondary transplant recipients.

Higher levels of murine  $\alpha_2$ : human  $\beta^4$  tetramers were obtained in peripheral blood samples from recipients of TNS9-transduced Hbb<sup>th3/+</sup> bone marrow (21±3% of total haemoglobin, n=5, than with Hbb<sup>+/+</sup> bone marrow (6±4%, n=10). The two groups showed comparable peripheral blood vector copy numbers and levels of human  $\beta$ -globin RNA ( $0.8 \pm 0.2$  compared with  $0.8 \pm 0.6$ , and  $16.8 \pm 6\%$  compared with  $10.8 \pm 7\%$ , respectively). This observation is consistent with a competitive advantage of murine  $\beta$ -globin over human  $\beta$ -globin in associating with murine  $\alpha$ -globin<sup>22</sup>. In thalassaemic patients, added human  $\beta$ -chain synthesis would improve the  $\alpha$ : $\beta$  chain imbalance and thus increase red cell survival and ameliorate the ineffective erythropoiesis in these patients. In patients with sickle cell disease, transduced  $\beta^4$  chains are expected to have an advantage over the  $\beta^S$  chains produced by both endogenous genes in competing for the available  $\alpha$ -chains<sup>23</sup>. Given that patients with S/ $\beta$ -thalassaemia whose HbA represents 10-30% of their total haemoglobin are very mildly affected<sup>1,24</sup>, the clinical benefit of such an intervention would be highly significant.

## EXAMPLE 7

To investigate long-term expression of the transduced human  $\beta$ -globin genes and its therapeutic efficacy, we generated bone marrow chimeras engrafted with TNS9-transduced Hbb<sup>th3/+</sup> bone marrow cells (n=5) and studied them over a 40-week period.

Donor bone marrow was flushed from the tumors of 8- to 16-week old male c57/BL6 or Hbb<sup>th3/+</sup> mice<sup>23</sup> obtain from Jackson Laboratories (Bar Harbor, Me.) that had been injected intravenously (IV) 6 days earlier with 5-fluorouracil (5-FU) 150 mg/kg body weight obtained from Pharmacia (Piscataway, N.J.). Bone marrow cells were resuspended in X-VIVO-15 serum-free medium and supplemented with 10 ng/mL interleukin-1 $\alpha$  (IL-1 $\alpha$ ), 100 U/mL IL-3, 150 U/mL

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IL-6, 10 ng/mL, Kit ligand obtained from Genzyme (Cambridge, Mass.), 0.5 mM  $\beta$ -mercaptoethanol obtained from Sigma (St. Louis, Mo.), 200-mM L-glutamine, 100 IU/mL penicillin, and 100  $\mu$ g/mL streptomycin. Bone marrow cells were then pelleted and resuspended in serum-free medium containing concentrated lentiviral supernatant and supplemented with 8 mg/mL polybrene (Sigma), 200 mM L-glutamine, 100 U/mL penicillin, 100  $\mu$ g/mL streptomycin and cytokines as above, and cultured for 8 hours. Transduced bone marrow cells ( $5 \times 10^5$ ) were then injected IV into each of the irradiated female recipients to establish bone marrow chimeras. Recipient mice (11- to 14-week-old C57/BL6 or Hbb $^{th3/+}$  mice) were irradiated with 10.5 Gy (Split dose  $2 \times 5.25$  Gy) on the day of transplantation.

Age-matched chimeras engrafted with eGFP-transduced Hbb $^{th3/+}$  (n=5) and Hbb $^{+/+}$  (n=5) bone marrow cells served as controls. Vector copy number was monitored in peripheral blood by quantitative Southern blot analysis, and found to remain stable, between 0.5 and 1.0 copy/cell on average (data not shown). Protein expression was assessed by quantitative hemoglobin analysis, to measure the proportion of hemoglobin tetramers that incorporate human  $\beta^4$  (Hbb $^{hu}$ , mu  $\alpha_2$ :hu $\beta^4_2$ ) or murine  $\beta$ -globin (Hbb $^{mu}$ , mu $\alpha_2$ :mu $\beta 2$ ), and immunofluorescence, to determine the fraction of mature RBCs that contain human  $\beta^4$  protein. Transgenic mice bearing one copy of a 230-kb yeast artificial chromosome encompassing the entire human  $\beta$ -globin-like gene cluster<sup>28</sup> served as reference, showing 14% of their total hemoglobin incorporating human  $\beta^4$  and 100%  $\beta^4$ +RBCs<sup>19,28</sup>. Hbb $^{hu}$  accounted for 19% to 22% of the total hemoglobin in TNS9 chimeras. These levels remained stable up to 40 weeks after transplantation. Over this same time period, the proportion of mature peripheral RBCs expressing human  $\beta^4$  also remained elevated and stable (about 70% to 80%), as shown by dual staining of human  $\beta^4$  and TER-119.

## EXAMPLE 8

## Long-Term Amelioration of Anemia

The stability of TNS9-encoded  $\beta^4$  expression detected in peripheral blood suggested that long-term hematologic and systemic therapeutic benefits could be obtained. To investigate whether Hbb $^{hu}$  production would suffice to treat the anemia, we closely monitored hemoglobin parameters over 40 weeks. The marked increase in hemoglobin concentration, RBC counts, and hematocrit was sustained throughout this time period. Control mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  bone marrow cells remained severely anemic, indicating that the transplantation procedure itself did not alter the anemic state. The reticulocyte counts decreased to 5% to 8% in TNS9 treated-chimeras, compared to 19% to 21% in control eGFP-treated Hbb $^{th3/+}$  chimeras and age-matched Hbb $^{th3/+}$  mice, suggesting an increase in RBC life span and a decrease in erythropoietic activity.

## EXAMPLE 9

To determine the impact of sustained human  $\beta$ -globin gene expression on hematopoiesis, we studied the degree of splenomegaly (enlargement of the spleen) and EMH in 1-year-old chimeras and age-matched control mice. Spleen weights measured in Tns9-treated Hbb $^{th3/+}$  chimeras were indistinguishable from recipients of eGFP-transduced normal bone marrow, as were the total number of cells per spleen. In contrast, mice engrafted with eGFP-transduced Hbb $^{th3/+}$  bone marrow cells showed spleen weights and total cell num-

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bers that were about 3-fold greater. The correction of spleen weight in TNS9 bone marrow chimeras corresponded to a concomitant normalization in total hematopoietic progenitor cell content. Spleen CFU-Es, BFUEs, and CFUs-GM were reduced to levels measured in recipients of eGFP-transduced Hbb $^{th3/+}$  bone marrow, whereas they remained elevated in control chimeras engrafted with eGFP-transduced Hbb $^{th3/+}$  bone marrow cells and in age-matched Hbb $^{th3/+}$  mice, as previously observed in another murine model of  $\beta$ -thalassemias.<sup>29</sup>

The regression of EMH was corroborated by morphologic examination of spleen and liver in long-term chimeras and age-matched controls. Histopathology of spleens of mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  marrow was virtually identical to that of spleen from control Hbb $^{th3/+}$  mice. Specifically, the red pulp was significantly expanded, accounting for 80% to 90% of the cross-sectional area, and densely occupied by nucleated erythroid precursors. The white pulp, based on cross-sectional area, was relatively decreased and the marginal zones were obscured by the large number of nucleated RBCs, reflecting major expansion of the red pulp and erythroid precursors. In TNS9-treated chimeras, the amount of red pulp was considerably decreased, accounting for only about 50% to 60% of the cross-sectional area. In addition, the number of nucleated erythroid precursors in the red pulp was decreased. Other immature hematopoietic cells were present in the red pulp, but much less frequently than in the spleens of control Hbb $^{th3/+}$  thalassemic mice. The livers from TNS9-treated chimeras were similar to those of the normal control mice in that no EMH was detected. In contrast, livers from mice engrafted with eGFP transduced Hbb $^{th3/+}$  bone marrow cells showed several small foci of intrasinusoidal EMH.

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## EXAMPLE 10

Toxic iron accumulation in the organs of thalassemic patients is a consequence of RBC destruction and increased gastrointestinal iron uptake. To determine whether sustained expression from the TNS9 vector reduced iron overload, we studied tissue sections of liver and heart, stained using Gomori iron stain. No iron deposition was seen in the livers of normal Hbb $^{+/+}$  control mice, whereas Hbb $^{th3/+}$  mice showed variable amounts of iron, including some large aggregates. TNS9-transduced treated chimeras demonstrated low to undetectable levels of iron in the livers, whereas iron was readily detected in the livers of all mice that received transplants of eGFP-transduced Hbb $^{th3/+}$  bone marrow cells. No iron accumulation was found in the heart of treated or control mice, as previously observed in another murine model of  $\beta$ -thalassemia,<sup>30</sup> in contrast to what is found in the human disease.<sup>1-3</sup>

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## EXAMPLE 11

To assess to efficacy of in vivo selection for cells transduced with globin and DHFR-encoding vectors in accordance with the invention, using antifolates the following alternative protocols are used. In protocol 1, the recipient mice are treated daily for 5 days with MTX (25 mg/Kg) and NBMPR-P (20 mg/Kg), starting 6 weeks after administration of transduced bone marrow cells. In protocol 2, the recipient mice are treated daily for 5 days with TMTX (40 mg/Kg) and NBMPR-P (20 mg/Kg), starting 6 weeks after administration of transduced bone marrow cells. In protocol 3, the recipient mice, conditioned with busulphan rather than with gamma-irradiation, are treated daily for 5 days with TMTX (40

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mg/Kg) and NBMPR-P (20 mg/Kg), starting 4 weeks after administration of transduced bone marrow cells. (TMTX (Neutrexin; US Bioscience); >MTX (Methotrexate LPF Sodium; Immunex); NBMPR-P (Nitrobenzylthioinosine 5'-monophosphate disodium salt; Alberta nucleoside therapeutics). Protocol 3 is in principle the most attractive protocol as the recipients are not irradiated and furthermore not treated with a "myeloablative conditioning regimen". They are treated with a relatively milder conditioning regimen consisting of a "non-myeloablative" dose of busulphan. It is hoped that, in combination with "in vivo selection" mediated by DHFR/TMTX, the recipients could be satisfactorily engrafted without receiving a harsh pre-transplant treatment. This would be the way to go for treating subjects with severe hemoglobinopathies.

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2. The cell of claim 1, wherein the mammalian hematopoietic progenitor cell or the stem cell is a human cell.
3. The cell of claim 2, wherein said vector further comprises a nucleic acid encoding a selectable marker.
- 5 4. The cell of claim 3, wherein the selectable marker is a dihydrofolate reductase or a mutant dihydrofolate reductase having increased resistance to antifolates as compared to a wild-type dihydrofolate reductase.
- 10 5. The cell of claim 1, wherein said functional globin is a mutant globin.
6. The cell of claim 1, wherein said functional globin is a wild-type globin.
7. The cells of claim 1, wherein said functional globin is a  $\beta$ -globin.

## SEQUENCE LISTING

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25

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27

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22

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<213> ORGANISM: mouse

&lt;400&gt; SEQUENCE: 4

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23

What is claimed is:

1. An isolated mammalian hematopoietic progenitor cell or an isolated mammalian stem cell comprising a recombinant lentiviral vector which comprises a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human  $\beta$ -globin locus control region (LCR), the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR, and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR, said vector providing expression of the globin in a mammal in vivo.

- 55 8. The cell of claim 7, wherein said  $\beta$ -globin is a human  $\beta$ -globin.
9. The cell of claim 1, wherein said functional globin is a  $\gamma$ -globin.
10. The cell of claim 1, wherein said functional globin is an  $\alpha$ -globin.
- 60 11. A method for making a mammalian hematopoietic progenitor cell or a mammalian stem cell composition which comprises
  - (a) preparing a recombinant lentiviral vector comprising a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments

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obtainable from a human  $\beta$ -globin locus control region (LCR), the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR, and a BamHII and BanII, HS4-spanning nucleotide fragment of said LCR, said vector providing expression of the globin in a mammal *in vivo*; and

(b) obtaining hematopoietic progenitor cells or stem cells from the mammalian individual, and transducing the cells with the recombinant vector.

12. The method of claim 11, wherein said vector further comprises a nucleic acid encoding a selectable marker.

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5      13. The method of claim 12, wherein the selectable marker is a dihydrofolate reductase or a mutant dihydrofolate reductase having increased resistance to antifolates as compared to a wild-type dihydrofolate reductase.

14. The method of claim 13, which further comprises performing selection using an antifolate on the transduced cell.

15. The method of claim 11, wherein said functional globin is a human  $\beta$ -globin.

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# EXHIBIT C

## Gene Therapy Hits a Peculiar Roadblock: A Virus Shortage

By Gina Kolata

Nov. 27, 2017

Eager to speed development of revolutionary treatments, the Food and Drug Administration recently announced that it would expedite approval of experimental gene therapies. But the regulatory process may not be the biggest obstacle here.

Biotech companies have exciting plans to introduce treatments that may be transformative, sometimes curing genetic diseases with a single treatment. And the firms are itching to test their products.

But they are struggling to obtain a critical component of the therapy: the disabled viruses used to slip good genes into cells that lack them.

This delivery system lies at the heart of many forms of gene therapy; without the disabled viruses, there is no treatment. But manufacturing them is costly and onerous.

The genes intended to fix a defect in the body are carried into each cell by a modified virus, usually a disabled version of an adenovirus or a lentivirus. These viruses must be custom-made in specialized facilities for each treatment.

Few gene-therapy companies have the factories or expertise to make the viruses for use in clinical trials, where standards are exacting and comprehensive. The firms that can do it are swamped with orders and requests.

The result is a logjam. Firms exploring new gene therapies may wait for years in line for bespoke viruses, said Dr. Jim Wilson, director of the gene therapy program at the University of Pennsylvania's Perelman School of Medicine.

"It's a real issue," said Udit Batra chief executive of MilliporeSigma, which makes viruses under contract for drug companies.

MilliporeSigma and other such manufacturers, he added, are "oversubscribed, although companies like ourselves have doubled capacity to keep up with the demand."

One of the few big companies producing a gene therapy, Novartis, recently got approval from the F.D.A. to market a treatment for a rare blood cancer.

But to get the viruses it needed, Novartis signed up years in advance with Oxford BioMedica, agreeing to three contracts starting in 2013 that, with incentives, add up to as much as \$195.2 million and that included a provision to pay Oxford a share of the royalties when the drug was approved.

Only a few hundred patients a year might need Novartis's treatment, and the company is charging \$475,000 for the one-time therapy.

Other gene therapy companies are not always able to afford the manufacturing costs or find a manufacturer. Some have taken to buying slots in virus production queues years in advance — like buying a nonrefundable airline ticket long before your vacation and hoping you can get away when the time comes.

Other firms are hedging their bets. Worried that production at one company will fail — as can happen with the finicky viruses — they buy places in line at two contract companies.

Still other biotechs have simply been shut out, unable to get their viruses made.

Then there is BioMarin, one of the larger and more successful biotech companies, which decided to spend several hundred million dollars to build its own virus-manufacturing plant. It does not plan to make viruses for anyone but itself.

"We don't want to be in a queue, that's for sure," said Robert Baffi, head of technical operations at BioMarin. The new facility also will give the company complete control over manufacturing, he added.

### A Difficult Road

The process of developing a gene therapy usually starts with academic researchers who do the preliminary tests. For the viruses they need, they often turn to a few academic medical centers with expertise in the requirements for early clinical research.

But there, too, demand far exceeds capacity. At Indiana University, “we are backed up through 2018,” said Dr. Kenneth Cornetta, a professor of molecular and medical genetics.

After a gene therapy gets through initial tests in an academic setting, researchers may license it to a biotech company or form their own small company. Then they have to find a manufacturer who will make their viruses according to the exacting standards required for treating patients.

Delays arise at every step. The contract virus-maker has to translate the small-scale production used for research purposes into a recipe for commercial production, where standards are extensive and documentation exhaustive. And the maker has to negotiate a contract to do all this.

Those two steps can easily take a year, said John Dawson, chief executive of Oxford BioMedica. When the contractor finally is ready to start making the viruses, it can be six months to a year before they are ready — assuming there are no glitches along the way.

Manufacturing custom-made viruses can cost biotech firms a third or more of their development budget, even for diseases so rare that they expect to treat only a dozen or so patients in their final study, Dr. Wilson said.

The gene therapy companies often have no drugs on the market and need money. But investors have become wary of companies that do not have a ready source of viruses.

“You’ve got to believe that every time someone gives a pitch to an investor, the investor will say, ‘What are you doing about manufacturing?’” Dr. Wilson said.

The whole development enterprise has become nerve-racking, researchers said. “You don’t know until the end that you have a product that is good enough to be used in a treatment,” said Dr. David Williams of Harvard.

Or, as officials at Bluebird Bio can attest, whether you have any product at all.

The company was formed in 2010, hoping to show that gene therapy could work in adrenoleukodystrophy, a rare and fatal neurodegenerative disease that strike boys. That was before the virus production logjam had begun, and all seemed well. Bluebird gave a virus manufacturer its recipe for making needed viruses.

Then, said Nick Leschly, the company’s chief executive, he got bad news. Using Bluebird’s recipe, the manufacturing company said it was going to cost Bluebird a million dollars to create enough viruses to treat one patient.

The company scurried to find ways to improve the efficiency of its recipe. Finally, they were ready to start anew. Manufacturing began, but months later there was nothing to show for it.

“We got no virus,” Mr. Leschly said.

“It was an Apollo 13 moment,” he added. “We put everyone in a room and said, ‘We have to figure this out. Everything at the company is now stopped. Nothing can be done without virus.’”

They finally found the source of the problem — the acidity of the solution used to grow the viruses was slightly off, killing them.

While the recipe for making viruses can affect prices, the cost of a new treatment also depends on how many patients will take the drug and how many cells from each patient must be altered by a virus.

If a company wanted to deliver a gene therapy to the lung or liver, where the organ’s “surface area is huge,” the current price could be as much as \$3 million per patient — “commercially unviable,” said Mr. Dawson of Oxford BioMedica.

Oxford is improving its methods, he said, and should soon be able to cut that cost to approximately \$300,000 per patient. Methods are improving, Mr. Dawson said, and his expectation is that it might cost a mere \$30,000 for the viruses in the future.

The costs of testing the drug and marketing it are, of course, out of his hands.

# EXHIBIT D

**press release**[!\[\]\(deff98e7d21b22121d016f5c2fa86c38\_img.jpg\) View printer-friendly version](#)<< [Back](#)

## FDA Grants Breakthrough Therapy Designation to LentiGlobin for Treatment of Beta-Thalassemia Major

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 2, 2015-- bluebird bio, Inc. (Nasdaq:BLUE) a clinical-stage company committed to developing potentially transformative gene therapies for severe genetic and rare diseases, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to LentiGlobin® BB305 Drug Product for the treatment of transfusion-dependent patients with beta-thalassemia major.

LentiGlobin BB305 Drug Product aims to treat beta-thalassemia major and severe sickle cell disease by inserting a functional human beta-globin gene into the patient's own hematopoietic stem cells *ex vivo* and then returning those modified cells to the patient through an autologous stem cell transplantation.

"The FDA's Breakthrough designation of LentiGlobin highlights that new therapies are needed for the treatment of patients with beta-thalassemia major, especially treatments with the potential to meaningfully reduce or liberate patients from transfusion dependence," said David Davidson, M.D., chief medical officer of bluebird bio. "Our early clinical data investigating the use of LentiGlobin in patients with multiple genotypes of beta-thalassemia major, including beta-0/beta-0, the most severe genotype, are very encouraging, and we remain on track to complete enrollment in the Northstar and HGB-205 studies in 2015. In light of the Breakthrough designation, we look forward to working even more closely with the FDA to expedite the development of LentiGlobin for the treatment of beta-thalassemia major."

The FDA's Breakthrough Therapy designation is intended to expedite the development and review of a drug candidate that is planned for use to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The benefits of Breakthrough Therapy designation include the same benefits as Fast Track designation, plus an organizational commitment involving FDA's senior managers with more intensive guidance from the FDA. Breakthrough Therapy designation does not however change the standards for approval.

The Breakthrough Therapy designation is supported by data from the ongoing Phase 1/2 Northstar (HGB-204) and HGB-205 studies of LentiGlobin. Findings in eight subjects with beta-thalassemia major were presented at the 56th Annual Meeting of the American Society of Hematology (ASH) in December 2014. In the first four subjects, each of whom had at least three months of follow up, treatment resulted in sufficient hemoglobin production to reduce or eliminate the need for transfusion support among patients with beta-thalassemia major who would otherwise require chronic blood transfusions. These data consisted of the first five subjects treated in bluebird bio's ongoing Northstar Study and the first three subjects from its HGB-205 study. These included the first beta-thalassemia subjects with the beta-0/beta-0 genotype to be treated with LentiGlobin BB305 drug product. The HGB-205 study also included the first subject with sickle cell disease to be treated with gene therapy.

### **About bluebird bio, Inc.**

With its lentiviral-based gene therapy and gene editing capabilities, bluebird bio has built an integrated product platform with broad potential application to severe genetic diseases and T cell-based immunotherapy. bluebird bio's clinical programs include Lenti-D™, currently in a Phase 2/3 study, called the Starbeam Study, for the treatment of childhood cerebral adrenoleukodystrophy, and LentiGlobin®, currently in three clinical studies: a global Phase 1/2 study, called the Northstar Study, for the treatment of beta-thalassemia major; a single-center Phase 1/2 study in France (HGB-205) for the treatment of beta-thalassemia major or severe sickle cell disease; and a separate U.S. Phase 1 study for the treatment of sickle cell disease (HGB-206). bluebird bio also has a preclinical CAR T cancer immunotherapy program in collaboration with Celgene Corporation, as well as discovery research programs utilizing megaTALs/homing endonuclease gene editing technologies.

bluebird bio has operations in Cambridge, Massachusetts, Seattle, Washington, and Paris, France. For more information, please visit [www.bluebirdbio.com](http://www.bluebirdbio.com).

### **Forward-Looking Statements**

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the potential efficacy and safety of the Company's LentiGlobin product candidate and the regulatory pathway afforded by Breakthrough Designation by the FDA, in particular statements concerning the reduced or eliminated need for transfusion support in the four initial subjects treated with LentiGlobin drug product, statements concerning the Company's future plans with respect to LentiGlobin and its other product candidates and statements concerning anticipated enrollment rates and clinical milestones in 2015. It should be noted that the data for LentiGlobin announced from the Northstar and HGB-205 studies at the ASH Annual Meeting are preliminary in nature and the Northstar and HGB-205 studies are not completed. There is limited data concerning long-term safety and efficacy following treatment with LentiGlobin drug product. These data may not continue for these subjects or be repeated or observed in ongoing or future studies involving our LentiGlobin product candidate, including the HGB-205 Study, the Northstar Study or the HGB-206 study in sickle cell disease. It is possible that subjects for whom periodic transfusion support has been reduced or temporarily eliminated may receive transfusion support in the future. It should also be noted that Breakthrough designation does not change the standards for approval and is not a guarantee of success. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that the preliminary results from our clinical trials will not continue or be repeated in our ongoing clinical trials, the risk that previously conducted studies involving similar product candidates will not be repeated or observed in ongoing or future studies involving current product candidates, the risk of cessation or delay of any of the ongoing or planned clinical studies and/or our development of our product candidates, the risk of a delay in the enrollment of patients in the Company's clinical studies, the risk that our collaboration with Celgene will not continue or will not be successful, and the risk that any one or more of our product candidates will not be successfully developed and commercialized. For a discussion of other risks and uncertainties, and

other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the

section entitled "Risk Factors" in our most recent quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

**Availability of other information about bluebird bio**

*Investors and others should note that we communicate with our investors and the public using our company website ([www.bluebirdbio.com](http://www.bluebirdbio.com)), our investor relations website (<http://www.bluebirdbio.com/investor-splash.html>), including but not limited to investor presentations and FAQs, Securities and Exchange Commission filings, press releases, public conference calls and webcasts. You can also connect with us on Twitter @bluebirdbio, [LinkedIn](#) or our [YouTube](#) channel. The information that we post on these channels and websites could be deemed to be material information. As a result, we encourage investors, the media, and others interested in bluebird bio to review the information that we post on these channels, including our investor relations website, on a regular basis. This list of channels may be updated from time to time on our investor relations website and may include other social media channels than the ones described above. The contents of our website or these channels, or any other website that may be accessed from our website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.*

Source: bluebird bio, Inc.

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# EXHIBIT E

**press release**[View printer-friendly version](#)[\*\*<< Back\*\*](#)

## **bluebird bio Announces FDA Priority Review of Biologics License Application for beti-cel Gene Therapy for Patients with β-thalassemia Who Require Regular Red Blood Cell Transfusions**

*If approved, beti-cel will be the first one-time treatment option to address the underlying genetic cause of disease*

*Current standard of care relies on regular red blood cell transfusions and iron management that carry the risk of progressive multi-organ damage and increased risk of morbidity and mortality*

*FDA set PDUFA date of May 20, 2022*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 22, 2021-- **bluebird bio, Inc.** (Nasdaq: BLUE) today announced that the U.S. Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for betibeglogene autotemcel (betti-cel) for priority review. Betti-cel is a potentially transformative gene therapy for adult, adolescent and pediatric patients with β-thalassemia across all genotypes who require regular red blood cell (RBC) transfusions. If approved, beti-cel will be the first one-time treatment that addresses the underlying genetic cause of disease for patients living with β-thalassemia in the U.S.—offering an alternative to regular RBC transfusions and iron chelation therapy. The agency has set a Prescription Drug User Fee Act (PDUFA) goal date of May 20, 2022.

"The FDA's acceptance of our BLA for beti-cel brings us one step closer to potentially providing a one-time treatment that can address the underlying cause of β-thalassemia and offer patients freedom from regular transfusions," said Andrew Obenshain, chief executive officer, bluebird bio. "It's also a critical milestone for bluebird bio as an independent severe genetic disease company. We are moving forward with great discipline and exceptional care to deliver on our commitments to patients and achieve our near-term goal of launching three first-in-class gene therapies in the U.S."

The BLA for beti-cel is based on data from bluebird bio's Phase 3 studies HGB-207 (Northstar-2) and HGB-212 (Northstar-3), the Phase 1/2 HGB-204 (Northstar) and HGB-205 studies, and the long-term follow-up study LTF-303. Together, these studies represent more than 220 patient-years of experience with beti-cel. As of March 9, 2021, the results include a total of 63 pediatric, adolescent and adult patients, including long-term efficacy and safety results in two patients with more than seven years follow-up. Additional data through August 2021 will be presented at the 63<sup>rd</sup> American Society of Hematology (ASH) Annual Meeting and Exposition, taking place December 11-14, 2021.

"For too long, people with β-thalassemia who rely on regular transfusions have had to live with extraordinary burdens associated with their disease. beti-cel works uniquely to help patients produce adult hemoglobin at normal or near-normal levels, which can eliminate their need for chronic transfusions and chelation that only temporarily relieve the symptoms of anemia and are associated with serious health risks and reduced quality of life," said Anne-Virginie Eggimann, chief regulatory officer, bluebird bio. "This BLA acceptance represents the culmination of contributions from many, including the patients involved in the clinical program, their caregivers, and the study investigators. We look forward to working closely with the FDA to bring this treatment to patients in need."

The FDA previously granted beti-cel Orphan Drug status and Breakthrough Therapy designation.

### **About β-thalassemia**

β-thalassemia is a severe genetic disease for those requiring regular red blood cell (RBC) transfusions, caused by mutations in the β-globin gene, which may cause significantly reduced adult hemoglobin (Hb). This can result in severe anemia and lifelong dependence on RBC transfusions. Patients who require regular RBC transfusions to maintain adequate Hb levels typically undergo the 4-7-hour process every 3-4 weeks. While transfusions temporarily relieve symptoms associated with severe anemia, including fatigue, weakness, and shortness of breath, they do not address the underlying genetic cause of β-thalassemia and can lead to unavoidable iron overload and serious complications, including progressive multi-organ damage and organ failure. Iron overload resulting from β-thalassemia or ongoing RBC transfusions requires chronic treatment with chelation therapy; even with chelation therapy, some patients remain significantly iron overloaded, and only 63% of patients are adherent, due in part to tolerability issues. Despite advances in treatment and improved transfusion techniques, people with β-thalassemia who require regular transfusions have an increased risk for morbidity and mortality.

### **About betibeglogene autotemcel (betti-cel)**

beti-beglogene autotemcel (betti-cel) (pronounced BEH tee cell) is a one-time gene therapy custom-designed to treat the underlying cause of β-thalassemia in patients who require regular red blood cell (RBC) transfusions. Betti-cel adds functional copies of a modified form of the β-globin gene ( $\beta^{\text{A-T87Q}}$ -globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs) in order to correct the deficiency of adult hemoglobin that is the hallmark of β-thalassemia. Once a patient has the  $\beta^{\text{A-T87Q}}$ -globin gene, they have the potential to produce beti-cel-derived adult hemoglobin ( $\text{HbA}^{\text{T87Q}}$ ) at levels that may eliminate the need for transfusions. In Phase 3 beti-cel studies, 89% (32/36) of evaluable patients across all ages and genotypes, including pediatric patients as young as four years of age and those with the most severe ( $\beta^0/\beta^0$ ) genotypes, achieved transfusion independence, which is defined as no longer needing RBC transfusions for at least 12 months while maintaining a weighted average Hb of at least 9 g/dL.

betti-cel is manufactured using the BB305 lentiviral vector (LVV), a third-generation, self-inactivating LVV that has been studied for more than a decade across multiple therapeutic areas.

Adverse reactions considered related to beti-cel were uncommon and consisted primarily of non-serious infusion-related reactions that occurred on the day of infusion (e.g. abdominal pain, hot flush, dyspnea, tachycardia and non-cardiac chest pain) and cytopenias (e.g. thrombocytopenia, leukopenia and neutropenia). Pain in extremity shortly after treatment was also documented. One of these adverse events (AE) was a serious adverse event (SAE) of thrombocytopenia considered possibly related to beti-cel and has resolved.

The majority of AEs and SAEs in the beti-cel clinical development program were unrelated to beti-cel and consistent with the known side effects of HSC collection and busulfan conditioning regimen (including several SAEs of veno-occlusive disease that resolved with treatment).

The Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies evaluating beti-cel are ongoing; enrollment is complete, and all patients have been treated. bluebird bio is also conducting a long-term follow-up study, LTF-303, to monitor safety and efficacy for people who have participated in bluebird bio-sponsored beti-cel clinical studies through 15 years post-treatment.

#### **About bluebird bio, Inc.**

bluebird bio is pursuing curative gene therapies to give patients and their families more bluebird days.

With a dedicated focus on severe genetic diseases, bluebird has industry-leading clinical and research programs for sickle cell disease, β-thalassemia and cerebral adrenoleukodystrophy and is advancing research to apply new technologies to these and other diseases. We custom design each of our therapies to address the underlying cause of disease and have developed in-depth and effective analytical methods to understand the safety of our lentiviral vector technologies and drive the field of gene therapy forward.

Founded in 2010, bluebird has the largest and deepest ex-vivo gene therapy data set in the world—setting the standard for industry. Today, bluebird continues to forge new paths, combining our real-world experience with a deep commitment to patient communities and a people-centric culture that attracts and grows a diverse flock of dedicated birds.

For more information, visit [bluebirdbio.com](http://bluebirdbio.com) or follow us on social media at [@bluebirdbio](#), [LinkedIn](#), [Instagram](#) and [YouTube](#).

bluebird bio is a trademark of bluebird bio, Inc.

#### **bluebird bio Cautionary Statement Regarding Forward-Looking Statements**

*This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect bluebird bio's business, particularly those identified in the risk factors discussion in bluebird bio's Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. These risks and uncertainties include, but are not limited to: the risk that the efficacy and safety results from our prior and ongoing clinical trials will not continue or be repeated in our ongoing or planned clinical trials; the risk that additional insertional oncogenic or other safety events associated with lentiviral vector, drug product, or myeloablation will be discovered or reported over time; and the risk that any one or more of our product candidates, will not be successfully developed, approved or commercialized. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, bluebird bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.*

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# EXHIBIT F

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## **bluebird Provides Update on FDA Review Timelines for Betibeglogene Autotemcel (beti-cel) for Beta-Thalassemia and Elivaldogene Autotemcel (eli-cel) for Cerebral Adrenoleukodystrophy (CALD)**

*FDA PDUFA goal dates for both therapies extended by three months*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 18, 2022-- **bluebird bio, Inc.** (NASDAQ: BLUE) today announced that the US Food and Drug Administration (FDA) has extended the review period for the biologics licensing applications (BLA) for its lentiviral vector gene therapies – betibeglogene autotemcel (beti-cel) for β-thalassemia and elivaldogene autotemcel (eli-cel) for cerebral adrenoleukodystrophy (CALD). The revised PDUFA goal dates for beti-cel and eli-cel are August 19, 2022 and September 16, 2022, respectively.

The FDA extended the PDUFA goal dates for beti-cel and eli-cel to allow time to review additional clinical information previously submitted by the company in response to FDA information requests as part of its ongoing reviews. The information was deemed a major amendment. The extension of the FDA review timeline does not relate to new safety events for either beti-cel or eli-cel.

bluebird's BLA submission for beti-cel for adult, adolescent and pediatric patients with β-thalassemia across all genotypes who require regular red blood cell (RBC) transfusions was accepted by the FDA for priority review in November 2021. The FDA accepted the BLA for eli-cel for patients with cerebral adrenoleukodystrophy (CALD) under the age of 18 for priority review in December 2021. If approved, beti-cel and eli-cel would be the first lentiviral vector gene therapies for patients with severe genetic diseases in the United States.

"Gene therapies are complex, potentially transformative treatment options for those living with severe genetic diseases, and we all share a responsibility to be diligent for patients as we progress this novel field," said Andrew Obenshain, CEO, bluebird bio. "We look forward to continuing to work with the FDA on its ongoing reviews of beti-cel and eli-cel, and to bringing these therapies to patients with beta-thalassemia and cerebral adrenoleukodystrophy in the US later this year."

The extended PDUFA goal dates are not expected to impact the priority review status of either BLA or the potential for bluebird bio to be granted priority review vouchers upon approval of beti-cel and eli-cel in 2022. The FDA previously granted both beti-cel and eli-cel Orphan Drug status, Breakthrough Therapy designation and Rare Pediatric Disease designation.

bluebird also provided an update on the FDA's partial clinical hold for the lovitibeglogene autotemcel (lovo-cel) gene therapy clinical program for patients under the age of 18 with sickle cell disease. Consistent with the FDA's clinical hold process, the company has received written questions from the FDA and is continuing to evaluate what impact, if any, the partial clinical hold may have on its projected Q1 2023 timing for submitting the BLA. bluebird plans to provide an update with its annual results in February.

### **About betibeglogene autotemcel (beti-cel)**

betibeglogene autotemcel (beti-cel) (pronounced BEH tee cell) is a one-time gene therapy custom-designed to treat the underlying cause of β-thalassemia in patients who require regular red blood cell (RBC) transfusions. Beti-cel adds functional copies of a modified form of the β-globin gene ( $\beta^{A-T87Q}$ -globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs) in order to correct the deficiency of adult hemoglobin that is the hallmark of β-thalassemia. Once a patient has the modified β-globin gene, they have the potential to produce beti-cel-derived adult hemoglobin ( $HbA^{T87Q}$ ) at levels that may eliminate the need for transfusions. In Phase 3 beti-cel studies 89% (31/35) of evaluable patients across ages and genotypes, including pediatric patients as young as four years of age and those with the most severe  $\beta^0/\beta^0$  genotypes, achieved transfusion independence, which is defined as no longer needing RBC transfusions for at least 12 months while maintaining a weighted average Hb of at least 9 g/dL.

beti-cel is manufactured using the BB305 lentiviral vector (LVV), a third-generation, self-inactivating LVV that has been studied for more than a decade across two therapeutic areas.

Adverse reactions considered related to beti-cel consisted primarily of non-serious infusion-related reactions that occurred on the day of the infusion and cytopenias. One serious adverse event (SAE) of thrombocytopenia considered possibly related to beti-cel was reported and has resolved.

The majority of AEs and SAEs in the beti-cel clinical development program were considered to be unrelated to beti-cel by the Investigator and were consistent with known side effects of HSC collection and the busulfan conditioning regimen.

The Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies evaluating beti-cel are ongoing; enrollment is complete, and all patients have been treated. bluebird bio is also conducting a long-term follow-up study, LTF-303, to monitor safety and efficacy for people who have participated in bluebird bio-sponsored beti-cel clinical studies through 15 years post treatment.

A biologics license application (BLA) for beti-cel is under priority review by the FDA. The agency has set a Prescription Drug User Fee Act (PDUFA) goal date of August 19, 2022.

### **About elivaldogene autotemcel (eli-cel, Lenti-D®) gene therapy**

eli-cel uses ex vivo transduction with the Lenti-D lentiviral vector (LVV) to add functional copies of the *ABCD1* gene into a patient's own hematopoietic stem cells (HSCs). The addition of the functional *ABCD1* gene allows patients to produce the ALD protein (ALDP), which is thought to facilitate the breakdown of very long-chain fatty acids (VLCFAs). The expression of ALDP and effect of eli-cel is expected to be life-long. The goal of treatment with eli-cel is to stop the progression of CALD and, consequently, preserve as much neurological function as possible, including the preservation of motor function and communication ability. Importantly, with eli-cel, there is no need for donor HSCs from another person.

bluebird bio's clinical development program for eli-cel includes the completed pivotal Phase 2/3 Starbeam study (ALD-102) and the ongoing Phase 3 ALD-104 study, which has completed enrollment. Additionally, bluebird bio is conducting a long-term safety and efficacy follow-up study (LTF-304) for patients who have received eli-cel for CALD and completed two years of follow-up in ALD-102 or ALD-104. Clinical studies of eli-cel are currently on hold with the FDA. A biologics license application (BLA) for beti-cel is under priority review by the FDA. The agency has set a Prescription Drug User Fee Act (PDUFA) goal date of September 16, 2022.

#### **About lovitibeglogene autotemcel (lovo-cel; formerly LentiGlobin® for SCD, bb1111)**

lovitibeglogene autotemcel (lovo-cel) gene therapy is an investigational one-time treatment being studied for sickle cell disease (SCD), that is designed to add functional copies of a modified form of the β-globin gene ( $\beta^{A-T87Q}$ -globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs). Once patients have the  $\beta^{A-T87Q}$ -globin gene, their red blood cells (RBCs) can produce anti-sickling hemoglobin ( $HbA^{T87Q}$ ) that decreases the proportion of HbS, with the goal of reducing sickled RBCs, hemolysis, and other complications. bluebird bio's clinical development program for lovo-cel includes the completed Phase 1/2 HGB-205 and ongoing Phase 1/2 HGB-206 and Phase 3 HGB-210 studies. bluebird bio is also conducting a long-term safety and efficacy follow-up study (LTF-307) for people who have participated in bluebird bio sponsored clinical studies of lovo-cel.

The safety profile of the lovo-cel treatment regimen is predominately reflective of the known risks of autologous stem cell transplantation and myeloablative single-agent busulfan conditioning, as well as underlying SCD. Adverse drug reactions due to lovo-cel include hot flush, decreased blood pressure, acute myeloid leukemia (AML), and anemia.

As of February 17, 2021, a total of 49 patients have been treated with lovo-cel, with up to six years of patient follow-up, in the HGB-205 (n=3), HGB-206 (n=44), and HGB-210 (n=2) clinical studies. The HGB-206 total includes: Group A (n=7), B (n=2), and C (n=35), representing progressive adaptations to the manufacturing and treatment processes. In the Group C cohort of the Phase 1/2 HGB-206 study, no severe vaso-occlusive events (VOEs) were reported with up to 24 months of follow-up in patients with a history of at least four severe VOEs and at least six months of follow-up.

In the initial cohort (Group A) of the HGB-206 study, two patients treated with lovo-cel developed AML. After thorough investigations into the cases, bluebird bio determined that these were unlikely related to the insertion of bluebird's lentiviral vector (LVV) gene therapy for SCD.

For more information on lovo-cel studies, visit: <https://www.bluebirdbio.com/our-science/clinical-trials> or [clinicaltrials.gov](https://clinicaltrials.gov).

The FDA has granted orphan drug designation, fast track designation, regenerative medicine advanced therapy (RMAT) designation, and rare pediatric disease designation for lovo-cel.

lovo-cel is investigational and has not been approved in any geography.

#### **About bluebird bio, Inc.**

bluebird bio is pursuing curative gene therapies to give patients and their families more bluebird days.

With a dedicated focus on severe genetic diseases, bluebird has industry-leading clinical and research programs for sickle cell disease, β-thalassemia and cerebral adrenoleukodystrophy and is advancing research to apply new technologies to these and other diseases. We custom design each of our therapies to address the underlying cause of disease and have developed in-depth and effective analytical methods to understand the safety of our lentiviral vector technologies and drive the field of gene therapy forward.

Founded in 2010, bluebird has the largest and deepest ex-vivo gene therapy data set in the world—setting the standard for industry. Today, bluebird continues to forge new paths, combining our real-world experience with a deep commitment to patient communities and a people-centric culture that attracts and grows a diverse flock of dedicated birds.

For more information, visit [bluebirdbio.com](https://bluebirdbio.com) or follow us on social media at [@bluebirdbio](#), [LinkedIn](#), [Instagram](#) and [YouTube](#).

Lenti-D, LentiGlobin® for SCD, and bluebird bio are registered trademarks of bluebird bio, Inc.

#### **bluebird bio Cautionary Statement Regarding Forward-Looking Statements**

*This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements, including but not limited to our statements regarding our expectations for our interactions with the FDA and the timing for the regulatory approval and potential commercial launch for beti-cel and eli-cel, and regarding the partial clinical hold of lovo-cel. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect bluebird bio's business, particularly those identified in the risk factors discussion in bluebird bio's Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. These risks include, but are not limited to: the risk that the FDA's review of the BLAs for beti-cel and/or eli-cel may require one or more additional extensions; the risk that beti-cel and/or eli-cel may not be approved within the priority review timeframe or at all, and consequently the risk that we may not be eligible to receive the associated priority review voucher upon the approval of beti-cel and/or eli-cel; the risk that the extension of BLA review may impact the conduct and timelines of our other programs; the risk that resolving the partial clinical hold of lovo-cel may require us to collect additional data or information beyond what we currently expect; the risk that we may not be able to address the FDA's concerns regarding lovo-cel in the treatment of patients with sickle cell under the age of 18 quickly or at all; the risk that we may not*

be able to collect the manufacturing comparability data needed to support a BLA submission for lovo-cel on our projected timelines; the risk that our planned BLA submission for lovo-cel may be delayed or may be for a narrower indication or patient population than we expected; the risk that the efficacy and safety results from our prior and ongoing clinical trials will not continue or be seen in additional patients treated with our product candidates; the risk that additional insertional oncogenic or other safety events associated with lentiviral vector, drug product, or myeloablation will be discovered or reported over time; the risk that any one or more of our product candidates will not be successfully developed, approved or commercialized; and the risks related to the ongoing COVID-19 pandemic. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, bluebird bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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# EXHIBIT G

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## Exhibit 99.1

### **bluebird bio and apceth Biopharma Establish Commercial Drug Product Manufacturing Agreement**

**Cambridge, Mass., (USA) and Munich, Germany, December 15, 2016** – bluebird bio, Inc. ([Nasdaq: BLUE](#)), a clinical-stage company committed to developing potentially transformative gene therapies for severe genetic diseases and T cell-based immunotherapies for cancer and apceth Biopharma GmbH ([www.apceth.com](#)), the global innovator and leader in the development of engineered mesenchymal stem cell (MSC) therapeutics and a successful and established contract development and manufacturing organization in the field of cell and gene therapy, announced today that they have entered into a strategic manufacturing agreement providing for the future European commercial production of bluebird bio's Lenti-D™ product candidate for cerebral adrenoleukodystrophy and its LentiGlobin™ product candidate for transfusion-dependent β-thalassemia.

This agreement follows a successful multi-year manufacturing relationship and provides bluebird bio with European commercial manufacturing capabilities, including dedicated production suites within apceth Biopharma's state-of-the-art GMP facility.

Under this multi-year agreement, apceth Biopharma will perform clinical manufacturing, process validation activities and commercial manufacturing for LentiGlobin and Lenti-D drug product to support the treatment of European patients with transfusion-dependent beta thalassemia and cerebral adrenoleukodystrophy, respectively.

"At bluebird, we are committed to not only developing potentially transformative therapies, but ensuring that we can deliver them to patients. For this reason, we are committed to investing in the capabilities and infrastructure necessary to support commercialization both in the U.S. and Europe," said Nick Leschly, chief bluebird. "By partnering with multiple organizations, including our valued partner apceth Biopharma, we are able to develop integrated capabilities in manufacturing that can position us to effectively bring our future commercial products to patients in need."

"We are very pleased to continue our successful contract manufacturing relationship with bluebird bio and plan to be the right partner in the future to enable product supply to European patients for clinical development and commercialization", said Christine Guenther, apceth Biopharma's CEO. "This long-term agreement confirms that apceth Biopharma is a valuable and reliable partner for our clients in the field of clinical and commercial cell and gene therapy manufacturing." Ulrike Verzetsnitsch, apceth Biopharma's CTO, added: "We are very proud that our customized GMP manufacturing solutions and our deep commitment to the client's needs and expectations are recognized



by bluebird bio, leading to a long-term strategic manufacturing relationship between our companies".

#### **About bluebird bio, Inc.**

With its lentiviral-based gene therapies, T cell immunotherapy expertise and gene editing capabilities, bluebird bio has built an integrated product platform with broad potential application to severe genetic diseases and cancer. bluebird bio's gene therapy clinical programs include its Lenti-D™ product candidate, currently in a Phase 2/3 study, called the Starbeam Study, for the treatment of cerebral adrenoleukodystrophy, and its LentiGlobin™ BB305 product candidate, currently in four clinical studies for the treatment of transfusion-dependent β-thalassemia and severe sickle cell disease. bluebird bio's oncology pipeline is built upon the company's leadership in lentiviral gene delivery and T cell engineering, with a focus on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR T) and T cell receptor (TCR) therapies. bluebird bio's lead oncology program, bb2121, is an anti-BCMA CAR T program partnered with Celgene. bb2121 is currently being studied in a Phase 1 trial for the treatment of relapsed/refractory multiple myeloma. bluebird bio also has discovery research programs utilizing megaTALS/homing endonuclease gene editing technologies with the potential for use across the company's pipeline.

bluebird bio has operations in Cambridge, Massachusetts; Seattle, Washington; and Paris, France.

#### **About apceth Biopharma GmbH**

apceth Biopharma is a pioneering biopharmaceutical company with a pipeline of cell-based gene therapeutics for the treatment of major chronic diseases (chronic lung disease, metabolic and autoimmune diseases) and solid cancer. The company's proprietary platform technology is based on state-of-the-art genetic engineering of mesenchymal stem cells. apceth Biopharma is also a successful Contract Development and Manufacturing Organization for complex cell and gene therapy products with a high international reputation. Based in Munich (Germany) in the heart of Europe, apceth Biopharma provides its proven expertise and state-of-the-art GMP facilities to the clients from around the world. apceth Biopharma was founded as apceth GmbH & Co. KG in 2007. The company is privately owned by its founders and private investors (Santo Holding GmbH and FCP Biotech Holding GmbH).

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**bluebird bio Forward-Looking Statements**

*This release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding bluebird bio’s LentiGlobin and Lenti-D product candidates and plans for their commercial manufacture in Europe. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks that the preliminary results from our clinical trials will not continue or be repeated in our ongoing or planned clinical trials, the risk of cessation or delay of any of the ongoing or planned clinical studies or the development of our product candidates, the risk of a delay in the enrollment of patients in our clinical studies and the risk that any one or more of our product candidates will not be successfully developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our most recent quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.*

# EXHIBIT H

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**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, DC 20549**  
**FORM 10-K**

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission File Number: 001-35966

**bluebird bio, Inc.**

(Exact Name of Registrant as Specified in Its Charter)

**Delaware**

(State or Other Jurisdiction of  
Incorporation or Organization)

**60 Binney Street**

**Cambridge, Massachusetts**

(Address of Principal Executive Offices)

**13-3680878**

(IRS Employer  
Identification No.)

**02142**

(Zip Code)

**(339) 499-9300**

(Registrant's Telephone Number, Including Area Code)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. **Yes**  **No**

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. **Yes**  **No**

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. **Yes**  **No**

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). **Yes**  **No**

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). **Yes**  **No**

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 30, 2018, the last business day of the registrant's most recently completed second quarter, was \$7,882,817,517.

As of February 15, 2019, there were 54,951,177 shares of the registrant's common stock, par value \$0.01 per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive Proxy Statement relating to its 2019 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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#### **FORWARD-LOOKING STATEMENTS**

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the initiation, timing, progress and results of our preclinical and clinical studies, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical studies;
- our ability to advance our viral vector and drug product manufacturing capabilities;
- the timing or likelihood of regulatory filings and approvals for our product candidates;
- the timing or success of commercialization of our product candidates, if approved;
- the pricing and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations and licenses;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

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**PART I****Item 1. Business****Overview**

We are a clinical-stage biotechnology company committed to developing potentially transformative gene therapies for severe genetic diseases and cancer. With our lentiviral-based gene therapy and gene editing capabilities, we have built an integrated product platform with broad therapeutic potential in a variety of indications. We believe that gene therapy for severe genetic diseases has the potential to change the way patients living with these diseases are treated by addressing the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. Our clinical programs in severe genetic diseases include our LentiGlobin® product candidate as a treatment for transfusion-dependent β-thalassemia, or TDT, and sickle cell disease, or SCD, and our Lenti-D™ product candidate as a treatment for cerebral adrenoleukodystrophy, or CALD. Our programs in oncology are built upon our leadership in lentiviral gene delivery and T cell engineering, with a focus on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. bb2121 and bb21217, our clinical-stage product candidates in oncology, are CAR T cell product candidates for the treatment of multiple myeloma.

We are developing our LentiGlobin product candidate for different genotypes of TDT and for SCD in the United States and the European Union, or EU. Both TDT and SCD are rare, hereditary blood disorders that often lead to severe anemia and shortened lifespans. In October 2018, we announced that the European Medicines Agency, or EMA, has accepted for review our marketing authorization application, or MAA, for our LentiGlobin product candidate for the treatment of adult and adolescent patients with TDT and non-β0/β0 genotypes. If we receive conditional approval in 2019, we expect to launch LentiGlobin in Europe and begin to generate product revenues. We plan to file a biologics license application, or BLA, in the United States in 2019 for the use of LentiGlobin in the treatment of adult and adolescent patients with TDT and non-β0/β0 genotypes. We are also engaged with the U.S. Food and Drug Administration, or FDA, and the EMA in discussions regarding our proposed development plans for LentiGlobin in SCD, with a potential first submission for regulatory approval in 2022.

We are developing our Lenti-D product candidate for CALD, a rare, hereditary neurological disorder that is often fatal. If our Lenti-D product candidate shows a sufficiently compelling treatment effect, and pending further discussion with regulatory authorities, the results from the phase 2/3 clinical study of our Lenti-D product candidate, called the Starbeam study, could potentially form the basis of a BLA submission in the United States and a MAA submission in the European Union. We anticipate a potential first submission for regulatory approval of our Lenti-D product candidate for the treatment of patients with CALD in 2019.

In collaboration with Celgene Corporation, or Celgene, we are developing our bb2121 and bb21217 product candidates in multiple myeloma, a hematologic malignancy that develops in the bone marrow and is fatal if untreated. We are co-developing and co-promoting the bb2121 product candidate in the United States with Celgene and we have exclusively licensed to Celgene the development and commercialization rights for the bb2121 product candidate outside of the United States. We and Celgene anticipate the first potential approval of the bb2121 product candidate for the treatment of relapsed and refractory multiple myeloma in the second half of 2020. We have exclusively licensed the development and commercialization rights for the bb21217 product candidate to Celgene, with an option for us to elect to co-develop and co-promote bb21217 within the United States.

**Our Gene Therapy Platform**

Our platform is based on lentiviral vectors which are used to introduce a functional copy of a gene to the patient's own isolated hematopoietic stem cells, or HSCs, in the case of our LentiGlobin and Lenti-D product candidates, or the patient's own isolated white blood cells which include T cells, in the case of our bb2121 and bb21217 product candidates. Additionally, we have developed a proprietary cell-based vector manufacturing process that is both reproducible and scalable. We believe our innovations in viral vector design and related manufacturing processes are important steps towards advancing the field of gene therapy and in realizing its full potential on a commercial scale.

Utilizing our platform, we are developing product candidates comprising the patient's own gene-modified HSCs and T cells. Clinical proof-of-concept already exists for allogeneic hematopoietic stem cell transplant, or HSCT, an approach of treating a patient with HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations, including difficulties in finding appropriate genetically-matched donors and carries the risk of transplant-related rejection, graft-versus-host disease, or GVHD, and mortality. Our approach is intended to address the significant limitations of allogeneic HSCT while utilizing existing stem cell transplant infrastructure and processes. Also, because our approach has the potential to drive sustained expression of the functional protein encoded by the gene insert after a single-administration, we believe the value proposition offered by our product candidates for patients, families, health care providers and payors would be significant.

Although our initial focus for severe genetic diseases is in TDT, SCD and CALD, and for cancer is in multiple myeloma, we believe our gene therapy platform has broad therapeutic potential in a variety of indications. We believe that our lentiviral vectors can be used to introduce virtually any gene into a cell and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using substantially the same process.

We also have discovery research programs utilizing our cell signaling and gene editing technology platform across our pipeline. For instance, we are exploring applications of our CAR and TCR T cell technologies in combination with novel proteins based on synthetic biology. These technologies may potentially allow our future T cell-based product candidates to detect the tumor microenvironment or, in the case of future CAR T cell product candidates, to be regulated by small molecules. In addition, we are focused on utilizing homing endonuclease and megaTAL gene editing technologies in a variety of potential applications and disease areas, including oncology, hematology and other diseases. Homing endonucleases and megaTALS are novel enzymes that provide a highly specific and efficient way to modify DNA sequences to edit or insert genetic components to potentially treat a variety of diseases.

## **Our Programs in Severe Genetic Diseases**

### **The LentiGlobin product candidate**

#### **$\beta$ -thalassemia**

##### *Overview*

$\beta$ -thalassemia is a rare genetic disease caused by a mutation in the  $\beta$ -globin gene resulting in the production of defective red blood cells, or RBCs. Genetic mutations cause the absence or reduced production of the beta chains of hemoglobin, or  $\beta$ -globin, thereby preventing the proper formation of hemoglobin A, which normally accounts for greater than 95% of the hemoglobin in the blood of adults. Hemoglobin is an iron-containing protein in the blood that carries oxygen from the respiratory organs to the rest of the body. Hemoglobin A consists of four chains-two chains each of  $\alpha$ -globin and  $\beta$ -globin. Genetic mutations that impair the production of  $\beta$ -globin can lead to a relative excess of  $\alpha$ -globin, leading to premature death of RBCs. The clinical implications of the  $\alpha$ -globin/  $\beta$ -globin imbalance are two-fold: first, patients lack sufficient RBCs and hemoglobin to effectively transport oxygen throughout the body and can become severely anemic; and second, the ineffective production of RBCs can lead to a range of multi-systemic complications, including but not limited to splenomegaly, marrow expansion, bone deformities, and iron overload in major organs.

The clinical course of  $\beta$ -thalassemia correlates with the degree of globin chain imbalance. Nearly 350 different mutations have been described in patients with  $\beta$ -thalassemia. Mutations can be categorized as those that result in no functional  $\beta$ -globin production ( $\beta^0$ ) and those that result in decreased functional  $\beta$ -globin production ( $\beta^+$ ). TDT refers to any mutation pairing that results in the need for chronic transfusions due to severe anemia. Affected patients produce as little as one to seven g/dL of hemoglobin (in contrast, a normal adult produces 12 to 18 g/dL of hemoglobin).

##### *Limitations of current treatment options*

In geographies where treatment is available, patients with TDT receive chronic blood transfusions to survive. These regimens consist of regular infusions with units of packed RBC, or pRBC, usually every two to five weeks, which are intended to maintain hemoglobin levels and control symptoms of the disease. While chronic blood transfusions can be effective at minimizing the symptoms of TDT, they often lead to unavoidable iron overload, which over time may lead to significant morbidity and mortality through iron-associated heart and liver toxicity. To help reduce iron overload-associated risks and resulting complications, patients must adhere to therapeutic iron chelation regimens to reduce the iron overload. Despite improvements in supportive care with transfusion and chelation, the overall life expectancy for a patient with TDT is significantly reduced compared to the general population. In addition, patient and caregiver quality of life can be significantly affected by complications associated with TDT and chronic disease management.

The only potentially curative therapy for  $\beta$ -thalassemia has been allogeneic HSCT, with best outcomes observed in pediatric patients with a matched sibling donor. However, allogeneic HSCT is associated with serious risks, some of which can be life threatening and result in death. Potential complications of allogeneic HSCT include a risk of engraftment failure in unrelated human-leukocyte-antigen, or HLA, matched patients, a risk of life-threatening infection, and a risk of GVHD, a common complication in which donor immune cells (white blood cells in the graft) recognize the cells of the recipient (the host) as "foreign" and attack them. As a result of these safety challenges, allogeneic HSCT can lead to significant mortality rates, particularly for patients treated with cells from a donor who is not a matched sibling, and in patients >11 years old. Consequently, we believe there is a need for an option that can address the underlying genetic cause of TDT for more patients, and that TDT is a life-shortening disease with a significant unmet medical need.

## **Sickle cell disease**

### *Overview*

Sickle cell disease, or SCD, is a hereditary blood disorder resulting from a mutation in the  $\beta$ -globin gene that causes polymerization of hemoglobin proteins, resulting in abnormal red blood cell function. The disease is characterized by anemia, vaso-occlusive events (a common complication of SCD in which there is severe pain due to obstructed blood flow in the small blood vessels of the body), cumulative damage to multiple organs, infections, stroke, overall poor quality of life and early death in a large subset of patients. Under low-oxygen conditions, which are exacerbated by the RBC abnormalities, the mutant hemoglobin polymerizes causing the RBCs to take on a sickle shape, which causes them to aggregate and obstruct small blood vessels, thereby restricting blood flow to organs resulting in pain, cell death and organ damage. If oxygen levels are restored, the hemoglobin can depolymerize and the RBCs will return to their normal shape, but over time, repeated sickling damages the cell membrane and the cells fail to return to the normal shape even in high-oxygen conditions.

### *Limitations of current treatment options*

Where adequate medical care is available, common treatments for patients with SCD largely revolve around management and prevention of acute sickling episodes. Chronic management may include hydroxyurea and, in certain cases, chronic RBC transfusions. Hydroxyurea is currently one of two medications approved for the treatment of SCD and is recommended for patients with recurrent moderate to severe painful crises, to reduce the frequency of painful crises. However, not all SCD patients respond to hydroxyurea, or are able to tolerate the cytotoxic effect of reduced white blood cell and platelet counts. A significant number of patients with SCD find it difficult to adhere to hydroxyurea treatment, and for most patients there is no effective long-term treatment. L-glutamine was approved by the FDA in 2017 as the second medication for the treatment of sickle cell disease and as such, there is limited long-term data available regarding its safety or efficacy.

RBC transfusion therapy can be utilized to maintain the level of sickle hemoglobin below 30% to 50%, which decreases sickling of RBCs, reduces the risk of recurrent stroke, and decreases the incidence of associated co-morbidities. While transfusion therapy can be critical in the management of acute disease, and can be vital in preventing some of the chronic manifestations of SCD, it does not provide equal benefit to all patients. Furthermore, in patients with SCD, it is associated with risks such as infection with blood-borne pathogens, alloimmunization, and adverse transfusion reactions that may lead to fatal outcomes. Additional complications of chronic transfusion include iron overload.

The only potentially curative therapy currently available for SCD is allogeneic HSCT, but it is limited to patients with severe disease manifestations and carries significant risk of transplant-related morbidity and mortality. Thus, this option is usually offered primarily to pediatric patients with available sibling-matched donors. It is particularly difficult to find suitable donors for individuals of African descent, and it is estimated that only a fraction of eligible patients undergo transplant. In light of these factors, we believe that SCD is a seriously debilitating and life-threatening disease with a significant unmet medical need.

## **Development of the LentiGlobin product candidate**

We are developing our LentiGlobin product candidate as a potential one-time treatment for both TDT and SCD. Our approach involves the *ex vivo* insertion of the normal  $\beta$ -globin gene with an amino acid substitution using a lentiviral vector into the patient's own HSCs to enable formation of normally functioning hemoglobin A and normal RBCs in patients. Importantly, this amino acid substitution, referred to as T87Q, also serves as a distinct biomarker used to quantify expression levels of the functional  $\beta$ -globin protein in patients with TDT and SCD, while also providing anti-sickling properties in the context of SCD. We refer to the cells that have undergone our *ex vivo* manufacturing process resulting in genetically modified HSCs as the LentiGlobin drug product, or our LentiGlobin product candidate.

We are conducting, or have conducted, the following clinical studies of our LentiGlobin product candidate to evaluate its safety and efficacy in the treatment of patients with TDT:

- Northstar study (HGB-204), a multi-site, international phase 1/2 study of patients with TDT. In March 2014, we announced that the first patient had been treated in this study. This study was completed in February 2018, and patients in this study were enrolled in a long-term follow-up protocol to assess safety and efficacy beyond the Northstar study follow-up period.
- Northstar-2 study (HGB-207), a multi-site, international phase 3 study of patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. In December 2016, we announced that the first patient had been treated in this study.
- Northstar-3 study (HGB-212), a multi-site, international phase 3 study of patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes or an IVS-I-110 mutation. In November 2017, we announced that the first patient had been treated in this study.

- HGB-205, a single-center phase 1/2 study in France of patients with TDT, which also enrolled patients with SCD. In December 2013, we announced that the first patient with TDT had been treated in this study.

We are conducting, or plan to conduct, the following clinical studies of our LentiGlobin product candidate to evaluate its safety and efficacy in the treatment of patients with SCD:

- HGB-206, a multi-site phase 1/2 study in the United States of patients with SCD. In October 2016, we announced amendments in the study protocol to incorporate several process changes, including using a refined drug product manufacturing process. In February 2017, we announced that the first patient had been treated under this amended study protocol.
- HGB-205, a single-center phase 1/2 study in France of patients with SCD which also enrolled patients with TDT. In October 2014, we announced that the first patient with SCD had been treated in this study.
- HGB-210, our planned multi-site, international phase 3 study of patients with SCD and a history of vaso-occlusive events, or VOEs. We anticipate that this study will have a comparable design to our HGB-206 study. We plan to initiate this study in 2019.

Our LentiGlobin product candidate has been granted Orphan Drug status by the FDA and EMA for both β-thalassemia and SCD. Our LentiGlobin product candidate was granted Fast-Track designation by the FDA for the treatment of β-thalassemia major and for the treatment of certain patients with SCD. The FDA has also granted Regenerative Medicine Advanced Therapy (RMAT) designation to our LentiGlobin product candidate for the treatment of SCD. The FDA has granted to our LentiGlobin product candidate Breakthrough Therapy designation for the treatment of transfusion-dependent patients with β-thalassemia major, and rare pediatric disease designation for the treatment of TDT. We are participating in the EMA's Adaptive Pathways pilot program (formerly referred to as Adaptive Licensing), which is part of the EMA's effort to improve timely access for patients to new medicines. In addition, the EMA has granted Priority Medicines (PRIME) eligibility for our LentiGlobin product candidate in the treatment of TDT.

In October 2018, we announced that the EMA accepted our marketing authorization application, or MAA, for LentiGlobin for the treatment of adolescents and adults with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. We anticipate a potential first conditional approval in the EU in 2019. Conversion to full approval may be subject to the successful completion of our Northstar-2 study and Northstar-3 study, or other studies we may be required to conduct, supportive long-term follow-up data and "real-world" post-approval monitoring data. Whether or not our clinical data are sufficient to support conditional, and ultimately full, approval will be a review decision by the EMA and European Commission. We also plan to submit a BLA in the United States in 2019 on the basis of the Northstar study and the Northstar-2 study of our LentiGlobin product candidate for the treatment of patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. In addition, if successful, we believe the data from our Northstar-3 study, together with data from our Northstar study and Northstar-2 study and HGB-205 study could be sufficient to form the basis for a BLA supplement submission in the United States, and a MAA variation submission in the EU, for our LentiGlobin product candidate for the treatment of patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes.

We are engaged with the FDA and the EMA in ongoing discussions regarding our proposed development plans for our LentiGlobin product candidate in SCD. Based on these discussions and clinical data for our LentiGlobin product candidate in SCD, we are exploring efficacy endpoints in our HGB-206 study and planned HGB-210 study that may allow us to pursue a more accelerated development path in the United States of our LentiGlobin product candidate for the treatment of patients with SCD who have a history of VOEs. Specifically, we are exploring the use of a primary efficacy endpoint based on  $\beta$ A-T87Q expression and total hemoglobin, and of a key secondary endpoint of frequency of VOEs. As expanded and modified in October 2018, the HGB-206 study will increase the overall set of clinical data regarding the relationship between anti-sickling hemoglobin and clinical outcomes, and has the potential to validate the new primary efficacy endpoint as a surrogate endpoint for other SCD clinical outcomes such as VOEs. Although we cannot be certain that the HGB-206 study and planned HGB-210 study will be sufficient to form the basis for a BLA submission in the United States or a MAA in Europe for the treatment of patients with SCD, these studies have been expanded, modified and planned with the goal of achieving a more accelerated development path for our LentiGlobin product candidate in the United States for the treatment of patients with SCD who have a history of VOEs, with a potential first submission for regulatory approval in 2022.

#### *Clinical results of the LentiGlobin product candidate*

- **Northstar study (HGB-204) - phase 1/2 study for the treatment of patients with TDT**

Our Northstar study is a single-dose, open-label, non-randomized, multi-site phase 1/2 clinical study in the United States, Australia and Thailand to evaluate the safety and efficacy of the LentiGlobin product candidate in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. In March 2014, we announced that the first patient had been treated in our Northstar study. In February 2018, we announced that the last patient in this study had completed the follow-up period under the Northstar study protocol.

Eighteen adults and adolescents were enrolled in the study. To be eligible for enrollment in this study, patients were between 12 and 35 years of age with a diagnosis of TDT and received at least 100 mL/kg/year of pRBCs or at least eight transfusions per year in each of the two years preceding enrollment. The patients were also eligible for allogeneic HSCT.

Efficacy was evaluated primarily by the production of  $\geq 2.0$  g/dL of hemoglobin A containing  $\beta$ A-T87Q-globin for the six-month period between 18 and 24 months post-treatment. Exploratory efficacy endpoints included pRBC transfusion requirements (measured in milliliters per kilogram) per month and per year, post-treatment. Safety evaluations performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Subjects were monitored by regular screening. Each patient remained on study for approximately 26 months from time of consent and then were enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.

In December 2018, we presented updated clinical data from our Northstar study at the 60th Annual Meeting of the American Society of Hematology, or ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date of September 14, 2018:

- Ten patients with non- $\beta$ 0/ $\beta$ 0 genotypes and eight patients with  $\beta$ 0/ $\beta$ 0 genotypes have undergone infusion with LentiGlobin drug product in the study.
- Of the ten patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes, eight patients achieved transfusion independence, meaning they had not received a transfusion for at least 12 months and maintained hemoglobin levels of  $\geq 9$  g/dL. These eight patients have maintained transfusion independence for a median duration of 38 months, with a range of 21 to 44 months. At the last study visit, total hemoglobin levels for these eight transfusion-independent patients were stable and ranged from 9.7 to 14.1 g/dL. HbAT87Q levels remained stable in these patients over time, for up to four years.
- Of the eight patients with TDT and a  $\beta$ 0/ $\beta$ 0 genotype, three patients achieved transfusion independence. These three patients had more than two years of follow up, and two of the three patients had follow-up for more than 3.5 years. All three patients maintained transfusion independence through their last study visit, with total hemoglobin levels ranging from 9.1 to 10.9 g/dL.
- An exploratory assessment was conducted to assess liver iron concentration in the 11 patients who have become transfusion independent in the Northstar study. Liver iron concentrations were measured at baseline and then at every 12 months after treatment. Over time, iron concentrations began to decrease in these 11 patients, with the largest decrease observed in the three patients who had at least 48 months of data available.
- The safety profile of the LentiGlobin drug product continues to be consistent with myeloblastic conditioning with single-agent busulfan. No grade 3 or higher drug product-related adverse events have been observed. The median time to platelet engraftment was 39.5 days, with a range of 19 to 191 days.

- **Northstar-2 study (HGB-207) - phase 3 study for the treatment of patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes**

Our Northstar-2 study is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the safety and efficacy of the LentiGlobin product candidate to treat patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. In December 2016, we announced that the first patient had been treated in our Northstar-2 study.

Approximately 23 patients will be enrolled in the study, consisting of at least 15 adolescent and adult patients between 12 and 50 years of age at enrollment, and at least eight pediatric patients less than 12 years of age at enrollment. To be enrolled, patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes must have received at least 100 mL/kg/year of pRBCs or at least eight transfusions per year for the past two years. All patients must be eligible for allogeneic HSCT, but without a matched family allogeneic HSCT donor. Subjects in our Northstar-2 study will be treated with our LentiGlobin product candidate manufactured using our refined drug product manufacturing process with the objective of increasing the vector copy number and the percentage of transduced cells, relative to the drug product manufacturing process used in our Northstar study.

The primary endpoint of this study is the proportion of treated patients who achieve transfusion independence, defined as weighted average hemoglobin levels  $\geq 9.0$  g/dL without any pRBC transfusions for a continuous period of at least 12 months at any time during the study after treatment. The secondary endpoints of this study are to quantify gene transfer efficiency and expression, and to measure the effects of treatment with the LentiGlobin drug product on transfusion requirements post-treatment and clinical events. Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.

In December 2018, we presented updated clinical data from our Northstar-2 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date of September 14, 2018:

- Sixteen patients with non- $\beta$ 0/ $\beta$ 0 genotypes, ranging from 8 to 34 years of age, have undergone infusion with LentiGlobin drug product in the study, including two pediatric patients and 14 adolescents/ adults.
- Eleven of these patients had at least three months of follow-up available. Ten of the 11 patients had stopped receiving transfusions and had hemoglobin levels ranging from 11.1 to 13.3 g/dL at the time of the last study visit (which occurred at 3 to 18 months post-treatment). HbAT87Q levels in these 10 patients ranged from 7.7 to 10.6 g/dL, which significantly contributed to total hemoglobin (ranging from 67 to 92 percent of total hemoglobin).
- An exploratory analysis was conducted with bone marrow from six patients with 12 months of follow-up after treatment. The samples were evaluated for cellularity and myeloid to erythroid ratio. In five patients, all of whom had stopped chronic transfusions, an increase in the myeloid to erythroid ratio was observed, suggesting improvement in red blood cell production. A low myeloid to erythroid ratio is a key feature of dyserythropoiesis, or abnormal bone marrow red blood cell production, characteristic of patients with TDT.
- The safety profile of LentiGlobin drug product continues to be consistent with myeloablative conditioning with single-agent busulfan, including serious adverse events (SAE) of veno-occlusive liver disease. One SAE of grade 3 thrombocytopenia was reported and considered possibly drug product-related.

• **Northstar-3 study (HGB-212) - phase 3 study for the treatment of patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes or IVS-I-110 mutation**

Our Northstar-3 study is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the efficacy and safety of the LentiGlobin product candidate to treat patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes or IVS-I-110 mutation. In November 2017, we announced that the first patient had been treated in our Northstar-3 study.

Approximately 15 patients who are less than 50 years of age at enrollment will be enrolled in the study. To be eligible, patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes or IVS-I-110 mutation must have received at least 100 mL/kg/year of pRBCs or at least eight transfusions per year for the past two years. All patients must be clinically stable and eligible to undergo HSCT, as well as having been treated and followed for at least the last two years in a specialized center that maintained detailed medical records, including transfusion history. Patients in our Northstar-3 study will be treated with our LentiGlobin product candidate manufactured using our refined drug product manufacturing process with the objective of increasing the vector copy number and the percentage of transduced cells, relative to the drug product manufacturing process used in our Northstar study.

The primary endpoint of this study is the proportion of treated patients who meet the definition of “transfusion reduction”, which is defined as demonstration of reduction in volume of pRBC transfusion requirements (in mL/kg) in the post-treatment time period of months 12 to 24 compared to the average annual transfusion requirement in the 24 months prior to enrollment. The secondary endpoints of this study are to measure the proportion of patients who meet the definition of “transfusion independence” and also quantify gene transfer efficiency and expression, and measure the effects of treatment with the LentiGlobin drug product on transfusion requirements post-treatment and clinical events. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol’s follow-up period.

In December 2018, we presented updated clinical data from our Northstar-3 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date of September 14, 2018, except as otherwise noted:

- Three patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes or IVS-I-110 mutation had been treated with LentiGlobin.
- All three patients, including a pediatric patient, had total hemoglobin of greater than 10 g/dL at their last assessment as of November 19, 2018. Patient 1 had no transfusions following LentiGlobin treatment and their last assessment at month 12, Patient 2 had their last transfusion 1.9 months post-treatment and last assessment at month six, Patient 3 had their last transfusion at 1.4 months post-treatment and last assessment at month three.
- The safety profile of LentiGlobin drug product continues to be consistent with myeloablative conditioning with single-agent busulfan. No grade 3 or higher drug product-related adverse events have been observed.

- **The HGB-206 study - phase 1/2 study for the treatment of patients with SCD**

Our HGB-206 study is a single-dose, open-label, non-randomized, multi-site phase 1/2 clinical study in the United States to evaluate the safety and efficacy of the LentiGlobin product candidate to treat SCD.

Up to 50 adult and adolescent patients will be enrolled in the study. Patients must be  $\geq 18$  years of age with a diagnosis of sickle cell disease, with either  $\beta S/\beta S$  or  $\beta S/\beta 0$  genotype. The sickle cell disease must be severe, as defined by recurrent severe VOEs, acute chest syndrome (ACS), history of an overt stroke, or echocardiographic evidence of an elevated tricuspid regurgitation jet velocity, an indicator of pulmonary hypertension, and patients must have failed to achieve clinical benefit from treatment with hydroxyurea. The patients must also be eligible for HSCT. We refer to the patients enrolled under the original study protocol as patients in "Group A." In October 2016, we announced amendments in the study protocol to incorporate several changes with the goal of increasing production of anti-sickling  $\beta$ -globin, such as increasing the percentage of transduced cells through manufacturing improvements, increasing target busulfan area under the curve, introducing a minimum period of regular blood transfusions prior to stem cell collection, and collecting HSCs from peripheral blood after mobilization with plerixafor rather than via bone marrow harvest. We refer to the patients enrolled under the amended study protocol utilizing HSCs from bone marrow harvest as patients in "Group B." We refer to the patients enrolled under the amended study protocol utilizing HSCs from peripheral blood after mobilization with plerixafor as patients in "Group C." In February 2017, we announced that the first patient had been treated under the amended study protocol.

The primary efficacy endpoint for this study is based on  $\beta A-T87Q$  expression and total hemoglobin, and the secondary efficacy endpoint for this study is the frequency of VOEs. Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any patient; and the characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Each patient will remain on study for approximately 26 months from time of consent and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow up period.

In December 2018, we presented updated clinical data from our HGB-206 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date as of September 14, 2018:

- Group A: A total of seven patients have undergone infusion with LentiGlobin drug product in Group A, with up to 39 months of follow-up. Consistent HbAT87Q production was observed ranging from 0.7 to 2.8 g/dL at last visit and patients maintained stable total hemoglobin levels ranging from 7.6 to 11.8 g/dL at last visit.
- Group B: Two patients have undergone infusion with LentiGlobin drug product in Group B, with up to 17 months of follow-up. HbAT87Q production was higher in Group B patients, ranging from 3.4 to 6.5 g/dL and total hemoglobin levels were stable at 11.0 to 12.3 g/dL at last visit.
- Group C: A total of nine patients have undergone infusion with LentiGlobin drug product in Group C.
  - In the four patients who were six months post treatment, HbAT87Q product ranged from 4.8 to 8.8 g/dL and were comparable to or exceeded the levels of HbS. These patients did not receive a blood transfusion during this time and had total hemoglobin levels ranging from 9.9 to 13.7 g/dL at their last visit.
  - No VOEs were reported (up to nine months post treatment with LentiGlobin). In an exploratory analysis, key markers of hemolysis, including reticulocyte counts, lactate dehydrogenase (LDH) and total bilirubin concentration had decreased compared to baseline.
  - To help assess the distribution of HbAT87Q in the red blood cells, we have developed an antibody that recognizes  $\beta S$ , the protein present in HbS. Using this antibody, the amount of  $\beta S$  was measured in the red blood cells obtained from healthy donors ( $\beta A/\beta A$ ), sickle cell trait donors ( $\beta S/\beta A$ ) and patients with sickle cell disease ( $\beta S/\beta S$ ). Clear and distinct distribution of  $\beta S$  was observed in these control samples, with highest expression in the  $\beta S/\beta S$  samples, followed by  $\beta S/\beta A$  and no expression of  $\beta S$  in the healthy donor ( $\beta A/\beta A$ ) samples. Initial results from two patients treated with LentiGlobin gene therapy, who were nine months post treatment, showed that nearly all their red blood cells had lower amounts of  $\beta S$  than the  $\beta S/\beta S$  and the  $\beta S/\beta A$  control samples. Given that these patients were no longer receiving any blood transfusions, this suggests  $\beta S$  expression was reduced in these patients due to the production of HbAT87Q following treatment with LentiGlobin.
- The safety profile of the LentiGlobin drug product continues to be consistent with myeloablative conditioning with single-agent busulfan. One SAE of myelodysplasia syndrome was reported in a patient who received LentiGlobin approximately three years ago in Group A. Analysis of the patient's cells showed no evidence of vector-mediated insertional oncogenesis, and the independent data monitoring committees, along with the treating physician, agreed the SAE was unlikely related to the drug product.

- **The HGB-205 study - phase 1/2 for the treatment of patients with TDT or SCD**

Our HGB-205 study is a single-dose, open-label, non-randomized, phase 1/2 clinical study at a single site in France to examine the safety and efficacy of our LentiGlobin product candidate in up to seven patients with a diagnosis of TDT or SCD. In December 2013, we announced that the first patient with TDT had been treated in our HGB-205 study and in October 2014 we announced that the first patient with SCD had been treated in our HGB-205 study.

Patients must be between five and 35 years of age with a diagnosis of TDT or SCD. To be enrolled, patients with TDT must have received at least 100 mL/kg/year of pRBCs per year for the past two years. Those with SCD must have failed to achieve clinical benefit from treatment with hydroxyurea and have an additional poor prognostic risk factor (e.g., recurrent VOEs or ACS). All patients must be eligible for allogeneic HSCT, but without a matched sibling allogeneic HSCT donor. This study is fully enrolled, with four patients with TDT and three patients with SCD enrolled in this study.

The primary objective of our HGB-205 study is to determine the safety, tolerability and success of engraftment of the LentiGlobin drug product. The secondary objectives of the study are to quantify gene transfer efficiency and expression, and to measure the effects of treatment with the LentiGlobin drug product on disease-specific biological parameters and clinical events. In the case of patients with TDT and SCD, this means the volume of pRBC transfusions, and for patients with SCD, it also means the number of VOEs and ACS in each patient, compared with the two-year period prior to treatment. Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.

In December 2017, we presented updated clinical data from our HGB-205 study in patients with SCD or TDT at the 59th Annual Meeting of the American Society of Hematology. All data presented and summarized below are as of the data cut-off date of September 20, 2017:

- All three patients with SCD showed rising HbAT87Q in the first six months following infusion.
  - Patient 1204 was 13 years old at study enrollment. At 30 months post-drug product infusion, this patient had a total hemoglobin level of 12.4 g/dL, of which 6.1 g/dL was HbAT87Q and 52 percent was anti-sickling hemoglobin. HbAT87Q concentration in this patient has remained stable since approximately nine months post-infusion. The patient continues to show marked clinical improvement.
  - Patient 1207 was 16 years old at study enrollment. At 9 months following drug product infusion, this patient had a total hemoglobin of 10.0 g/dL, of which 0.7 g/dL was HbAT87Q and 14 percent was anti-sickling hemoglobin. This patient had a pre-treatment history of frequent episodes of VOEs and ACS despite hydroxyurea prior to beginning regular transfusions. Patient 1207 had episodes of ACS and hospitalization at six and eight months post-treatment, and was treated with exchange transfusions.
  - Patient 1208 was 21 years old at study enrollment. At last follow-up (6.0 months), this patient had a total hemoglobin of 10.6 g/dL, of which 2.7 g/dL was HbAT87Q and 46 percent was anti-sickling hemoglobin. This patient had a pre-treatment history of frequent episodes of VOEs and ACS prior to beginning regular transfusions, and was still symptomatic while receiving regular transfusions. Following LentiGlobin treatment, Patient 1208 has had no episodes of VOEs or ACS (with six months follow-up).
- All four patients with TDT have remained free of chronic transfusions since shortly after receiving LentiGlobin drug product. Patient 1201 ( $\beta^0/\beta^E$  genotype) has been free of transfusions for 45.2 months with total hemoglobin of 10.1 g/dL at month 42, of which 6.7 g/dL was HbAT87Q. Patient 1202 ( $\beta^0/\beta^E$  genotype) has been free of transfusions for 40.1 months with total hemoglobin of 12.9 g/dL at month 42, of which 10.1 g/dL was HbAT87Q. Patient 1206 ( $\beta^0/\beta^E$  genotype) has been free of transfusions for 23.8 months with total hemoglobin of 11.1 g/dL at month 21, of which 8.0 g/dL was HbAT87Q. Subject 1203, who is homozygous for the severe  $\beta^+$  mutation IVS1-110, has been free of transfusions for 20.9 months with total hemoglobin of 8.7 g/dL at month 24, of which 6.7 g/dL was HbAT87Q. Three of four patients (1201, 1202 and 1206) were able to begin therapeutic phlebotomy. Patient 1202 subsequently discontinued iron chelation and phlebotomy.
- The safety profile of LentiGlobin drug product continues to be consistent with myeloablative conditioning with single-agent busulfan. No drug-product related adverse events have been observed.

## The Lenti-D product candidate

### *Adrenoleukodystrophy*

#### *Overview*

Adrenoleukodystrophy is a rare X-linked, metabolic disorder caused by mutations in the ABCD1 gene which results in a deficiency in adrenoleukodystrophy protein, or ALDP, and subsequent accumulation of very long-chain fatty acids, or VLCFA. VLCFA accumulation occurs in plasma and all tissue types, but primarily affects the adrenal cortex and white matter of the brain and spinal cord, leading to a range of clinical outcomes. The most severe form of ALD, the inflammatory cerebral phenotype, referred to as CALD, involves a progressive destruction of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of neurological function and eventual death in most patients. We estimate that approximately 35% to 40% of boys with ALD will develop CALD.

#### *Limitations of current treatment options*

Currently, the only effective treatment option for CALD is allogeneic HSCT. In this procedure, the patient is treated with HSCs containing a functioning copy of the gene contributed by a donor other than the patient. Allogeneic HSCT is an effective treatment option for patients in the earliest stages of cerebral disease, particularly if done using cells from an unaffected human leukocyte antigen (HLA)-matched sibling donor, which minimizes the risk associated with allogeneic HSCT. However, the majority of allogeneic HSCT procedures for CALD are carried out with non-sibling matched donor cells or partially matched related or unrelated donor cells including umbilical cord blood cells because a matched sibling donor is not available. While safety risks, including transplant-related morbidity and mortality, graft failure, GVHD, and opportunistic infections are of particular concern when transplants are performed in the absence of a matched sibling donor, the potential for life-threatening risks exists even when an HLA-matched sibling donor is available. Donor availability and transplant-related risks limit the broader use of allogeneic HSCT.

As the outcome of HSCT varies with clinical stage of the disease at the time of transplant, early diagnosis of CALD is important. In the United States, newborn screening for ALD was added in February 2016 to the Recommended Universal Screening Panel, a list of disorders that are screened at birth and recommended by the Secretary of the U.S. Department of Health and Human Services for states to screen as part of their state universal newborn screening program. Disorders are chosen based on evidence that supports the potential net benefit of screening, among other factors. An increasing number of states are including ALD testing in their state newborn screening programs.

#### *Development of the Lenti-D product candidate*

We are developing our Lenti-D product candidate as an autologous treatment of CALD, with the potential to provide the effectiveness seen with allogeneic HSCT, but without the immunologic risk. Our approach involves the *ex vivo* insertion of a functional copy of the ABCD1 gene via a lentiviral vector into the patient's own HSCs. Following engraftment, we expect the transduced HSCs to differentiate into other cell types, including macrophages and cerebral microglia, which produce functional ALDP. We believe that the functional ALDP can then enable the local degradation of VLCFAs in the brain, which in turn can stabilize the disease by preventing further cerebral inflammation and demyelination that are characteristics of CALD.

We are conducting the Starbeam study (ALD-102), a multi-site, international phase 2/3 study of our Lenti-D product candidate to evaluate its safety and efficacy in the treatment of patients with CALD. In early 2019, we intend to initiate our planned ALD-104 study, multi-site phase 3 study of our Lenti-D product candidate for the treatment of patients with CALD, to enable access following completion of enrollment in the Starbeam study, and to evaluate the suitability of an additional conditioning regimen for use with the Lenti-D product candidate.

Based on our discussions with the FDA and EMA, we believe that we may be able to seek approval for our Lenti-D product candidate for the treatment of patients with CALD on the basis of the clinical data from our ongoing Starbeam study, and the ongoing ALD-103 observational study. For the assessment of efficacy, we expect that the clinical results of the Starbeam study will be compared to a clinically meaningful benchmark based on the medical literature and data collected in ALD-101, a retrospective analysis that assessed the natural history of CALD as well as outcomes of patients with CALD who had received allogeneic HSCT. For the assessment of safety, we expect that the clinical results of the Starbeam study will be compared to data collected from the ALD-103 study, a multinational, multi-site, prospective and retrospective observational study that is running concurrently with the Starbeam study and is designed to evaluate outcomes of allogeneic HSCT in patients with CALD. We anticipate a potential first submission for regulatory approval of our Lenti-D product candidate for the treatment of patients with CALD in 2019. Lenti-D has been granted Orphan Drug status by the FDA and EMA for adrenoleukodystrophy. The FDA has granted Breakthrough Therapy designation and the EMA has granted PRIME eligibility to the Lenti-D product candidate for CALD.

**Clinical results of the Lenti-D product candidate**

- **Completed non-interventional retrospective study (the ALD-101 Study)**

CALD is a rare disease and as such, data on the natural history of the disease, as well as the efficacy and safety profile of allogeneic HSCT is limited in the scientific literature. In order to further characterize the natural history of CALD, describe outcomes after HSCT, and identify predictors of positive treatment outcomes, we performed a large, multicenter, retrospective chart review and collected data on 72 untreated CALD patients, and 65 CALD patients who received allogeneic HSCT. In the study, we collected survival, functional and neuropsychological assessments and neuroimaging data for both treated and untreated patients, as available; however, given the retrospective nature of the study, we were not able to collect comprehensive data for all patients. Additional analyses were conducted to gain further insight into ongoing risks and determinants of successful outcomes after HSCT, identify appropriate populations for treatment, and define endpoints that could be useful for future clinical studies.

- **Starbeam study (ALD-102) - phase 2/3 study for the treatment of patients with CALD**

Our Starbeam study is a single-dose, open-label, non-randomized, international, multi-site phase 2/3 study to evaluate the safety and efficacy of the Lenti-D drug product in males with CALD  $\leq$  17 years of age. We treated the first patient in the Starbeam study in the United States in October 2013. We announced that we achieved our enrollment target in September 2018.

In the study, patients must be age seventeen years or younger with a confirmed diagnosis of active CALD, including elevated levels of plasma VLCFA, a Loes score of 0.5 to  $\leq$  9, inclusive, evidence of gadolinium enhancement and an NFS  $\leq$  1. Patients with a willing, unaffected 10/10 HLA-matched sibling HSCT donor are excluded from the study.

The primary efficacy endpoint of the study is the proportion of patients who are alive and free of major functional disabilities (MFD) at 24 months post-treatment. MFDs, which represent end-stage disease, have been characterized as having the most significant impact on the ability of patients with CALD to function independently, representing unambiguous and profound neurologic degeneration. These MFDs are: loss of communication, no voluntary movement, cortical blindness, tube feeding, wheelchair dependence, and total incontinence. Secondary and exploratory endpoints include the following:

- Changes in neurologic function score (NFS), a 25-point scale used to evaluate the severity of gross neurologic dysfunction by scoring 15 neurological abnormalities across multiple domains.
- Changes in Loes score, a 34-point scale designed to objectively measure the extent of demyelination and atrophy in CALD patients, based on brain magnetic resonance imaging, or MRI, studies. Increasing Loes scores indicate worsening disease.
- Gadolinium enhancement (GdE). CALD can progress rapidly and is associated with severe inflammation and disruption of the blood brain barrier which can be detected by gadolinium enhancement on brain MRI. Evidence of gadolinium enhancement, referred to by clinicians as a gadolinium positive result, is highly predictive of rapid neurologic decline. However, while pre-transplant gadolinium status is clearly correlated with rapid disease progression, the kinetics of gadolinium enhancement after clinically successful HCST are not well understood. GdE was assessed by magnetic resonance imaging (MRI) every six months following transplant up to 24-months, and every 12 months thereafter.

The primary safety endpoint is the proportion of patients who experience either  $\geq$  Grade 2 acute GVHD or chronic GVHD by 2 years post-treatment. Additional safety evaluations include the following: success and kinetics of HSC engraftment, incidence of transplant-related mortality; detection of vector-derived replication-competent lentivirus; and characterization and quantification of events related to the location of insertion of the functional gene in target cells. Patients will be followed for 24 months post-treatment under this protocol. In accordance with applicable guidance from the FDA and EMA, we will be monitoring patients in a separate long-term follow up protocol to evaluate safety for up to 15 years, and will also monitor efficacy endpoints to demonstrate a sustained treatment effect.

In September 2018, we presented updated clinical data at the Society for the Study of Inborn Errors of Metabolism (SSIEM). All data presented and summarized below are as of the data cut-off date of April 25, 2018, except as otherwise indicated below:

- 31 patients are enrolled in the study. Of these 31 patients, 29 have been treated with Lenti-D and the median follow-up for all treated patients was 34 months, with a range of 0.4 to 54 months.
- 17 patients have completed 24 months of follow-up (median of 41.4 months, ranging from 13.4 to 54.0 months), of which 15 patients are alive and MFD-free. One patient withdrew from the study and was referred for allogeneic HSCT, and one died following rapid disease progression and development of MFDs beginning early in their participation in the study post-treatment.

- In the 15 patients who completed 24 months of follow-up, 14 were negative for GdE as of their last MRI. Eleven patients in the study had intermittent hazy re-emergence of GdE-positivity at various follow-up assessments, however, post-treatment GdE positivity was markedly reduced in intensity and does not appear to correlate with clinical outcome.
- In the 15 patients who met 24 months of follow up by April 25, 2018; 14 had an NFS score  $\leq 1$  at their last follow-up visit, and one patient had an increase in NFS from 1 to 2, due to vision impairment and non-febrile seizures.
- An additional 12 patients have received Lenti-D, but have not reached the primary endpoint of 24-month follow-up, there have been no MFDs reported. The median follow-up for this additional cohort of patients is 4.2 months, with a range of 0.4 to 11.7 months. Since SSIEM and as of the Annual Child Neurology Society Meeting in October 2018, one additional patient withdrew from the study at investigator discretion due to neuroimaging changes with no changes in neurological function noted.
- No acute or chronic GVHD has been reported post-Lenti-D treatment. The safety profile of Lenti-D is generally consistent with myeloablative conditioning with busulfan and cyclophosphamide. Three adverse events (AE) have been deemed potentially related to treatment with Lenti-D and include BK-mediated viral cystitis (grade 3), tachycardia (grade 1), and vomiting (grade 1).

- **The ALD-103 study - Observational study**

We are also conducting the ALD-103 study, an observational prospective and retrospective data collection study of 60 patients with CALD  $\leq 17$  years of age who received allogeneic HSCT. This study is ongoing and designed to collect efficacy and safety outcomes data in patients who have undergone allogeneic HSCT in a period that is contemporaneous with the Starbeam study. We anticipate that our Lenti-D product candidate safety and efficacy will be evaluated by the FDA and EMA in light of the data collected in the Starbeam study in conjunction with our retrospective observational ALD-101 study and our retrospective and prospective observational ALD-103 study.

In September 2018, we presented interim clinical data from the ALD-103 study at SSIEM. All data presented and summarized below are as of the data cut-off date of April 25, 2018:

- 41 pediatric patients were enrolled in the ALD-103 study and had undergone allogeneic HSCT. Thirty-one patients received cells from unrelated donors and 10 received cells from a related donor. The median baseline NFS for the group was 0.0, with a range of 0.0 to 4.0. The median Loes score was 3.0, with a range of 0.0 to 16.0. Twenty-five patients had early cerebral disease, defined as having evidence of cerebral disease established by GdE positivity or Loes score  $\geq 0.5$ , Loes score  $\leq 9.0$ , and NFS  $\leq 1$ .
- Initial results were in line with safety and efficacy outcomes reported in the literature for allogeneic HSCT in patients with CALD. Two-year Kaplan-Meier estimates of MFD-free survival post-allogeneic HSCT, were 78 percent for patients with early disease (n=25) and 71 percent for all patients (n=41).
- Transplant-related mortality was defined as death due to any transplantation-related cause other than disease progression. There were six transplant-related deaths at one year (14.6 percent); 2 among patients with early disease; none of the six patients had a matched sibling donor. Engraftment failure was reported in five patients (12 percent), all with early disease; none of these patients had a matched sibling donor and all received a second transplant.
- Of the 41 patients who received allogeneic HSCT, 34 percent (n=14) experienced either grade  $\geq 2$  acute GVHD or chronic GVHD. Twenty-five percent of patients who received cells from a matched sibling donor experienced either grade  $\geq 2$  acute GVHD or chronic GVHD.

#### **Our collaboration with Boston Children's Hospital in SCD**

We are collaborating with investigators at Boston Children's Hospital, or BCH, to advance a product candidate that utilizes a lentiviral vector delivering a short hairpin RNA, or shRNA, embedded in a microRNA, or miRNA, which is commonly known as a shMIR, to suppress the genetic target BCL11a to upregulate fetal hemoglobin to treat patients with SCD. We have an exclusive license to this program and the related intellectual property from BCH.

In December 2018, BCH presented initial clinical data from the investigator-initiated phase I study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized here are as of the data cut-off date of July 28, 2018. One patient had received treatment with BCL11a shMIR. In the patient's immature red blood cells, expression of the BCL11A protein was reduced by approximately 90 percent compared to levels prior to gene therapy. At 76 days following treatment this patient had a sustained total hemoglobin level of  $>10$  g/dL and, compared to what was observed pre-gene therapy, there was a notable absence of irreversibly sickled cells as assessed by peripheral blood smear, a blood test used to identify abnormalities in the number or shape of blood cells. The safety profile of the drug product was consistent with myeloablative conditioning, and there have been no product-related adverse events and no SCD-related complications.

### **Our preclinical research opportunities in severe genetic diseases**

We believe our current gene therapy platform will enable us to develop and test new vectors based on similar viral vector backbones that carry different gene sequences for other severe genetic diseases. In this way, we believe that we can advance products efficiently through preclinical into clinical development. We may consider research and development programs targeting other monogenic, genetic diseases that involve cells derived from HSCs for use in the *ex vivo* setting. These programs may involve severe genetic and rare diseases that could be developed and potentially commercialized on our own.

In addition, we believe our expertise in gene editing and cell transduction also provides an opportunity to develop new products for use in the *in vivo* setting. In this case, homing endonucleases and megaTALs that provide a highly specific and efficient way to modify DNA sequences to edit or insert genetic components would be delivered directly to the disease site (e.g., to the brain, liver or eye) or into the bloodstream of the patient and, *in vivo* deliver the genetic material to or modify those target cells. We believe *in vivo* gene editing opens up additional rare disease and large market indications where this approach is more appropriate for the disease and targeted cells.

### **Our Programs in CAR and TCR T Cell Technologies**

Like our programs for HSCs, our T cell-based immunotherapies use a customized lentiviral vector to alter T cells *ex vivo*, or outside the body, so that the T cells can recognize specific proteins or protein fragments on the surface of cancer cells in order to kill these diseased cells. T cells that have been genetically-engineered to make CAR or TCRs are designed to help a patient's immune system overcome survival mechanisms employed by cancer cells. CAR T cell technology directs T cells to recognize cancer cells based on expression of specific cell surface antigens, whereas TCR T cell technology provides the T cells with a specific T cell receptor that recognizes protein fragments derived from either intracellular or extracellular proteins which are displayed on the tumor cell surface. For both our CAR and TCR T cell technologies, we harvest a patient's white blood cells in a process called leukapheresis, activate certain T cells to grow and then use a lentiviral vector to transfer the gene sequences for the CAR or TCR construct into the T cell DNA. Once returned to the patient, these genetically engineered cells engage the target protein on the cancer cell, triggering a series of signals that result in tumor cell killing, the production of anti-cancer cytokines, and multiple rounds of cell division to greatly expand the number of these anti-cancer T cells in the patient. These engineered T cells have the natural "auto-regulatory" capability of normal T cells and once the tumor cells containing the target antigen are destroyed, the engineered T cells decrease in number, but with the potential to leave a smaller number of memory T cells in the body as a form of immune surveillance against potential tumor regrowth. The genetically-engineered T cells are designed to supplement a patient's immune system and may be further engineered to overcome immune evasion mechanisms employed by cancer cells.

Our CAR and TCR T cell technologies also bring genomic engineering tools to the immunotherapy field. For instance, we are exploring applications of our CAR and TCR T cell technologies in combination with novel proteins based on synthetic biology. These technologies may potentially allow our future T cell-based product candidates to detect the tumor microenvironment or, in the case of future CAR T cell product candidates, to be regulated by small molecules. In addition, using our gene editing technology, we potentially have a number of additional options to manipulate the genome of the cancer patient's T cells to further increase the specificity of the anti-tumor activity and to potentially make these cells even more potent. Specificity and potency are essential to the development of T cell therapies that can effectively treat solid tumor cancers such as breast, lung and colon cancer. Our cancer immunotherapy research group is staffed by scientists drawn from both industry and academic research centers that have pioneered the field of T cell therapy. This team is focused on the next generation of T cell engineering to discover and develop T cell product candidates to treat a variety of hematologic and solid tumor malignancies.

Our collaboration with Celgene focuses on CAR T cell product candidates directed against BCMA, a protein expressed on the surface of multiple myeloma cells, plasma cells and some mature B cells. We are developing, in collaboration with Celgene, our bb2121 and bb21217 product candidates with the goal of filing for regulatory approval in multiple myeloma on a global basis. We also have collaborations in the field of cancer with Regeneron Pharmaceuticals, Inc., or Regeneron, for the discovery, development, and commercialization of novel cell therapies; with Medigene AG, through its subsidiary Medigene Immunotherapies GmbH, to discover TCR product candidates; with Gritstone Oncology, Inc., to validate targets and discover TCR product candidates; and with TC Biopharm Limited, in the research and development of gamma delta CAR T cells.

### **The anti-BCMA CAR T cell product candidates: bb2121 and bb21217**

#### *Overview*

In collaboration with Celgene, we are developing the bb2121 and bb21217 product candidates, with the goal of filing for regulatory approval in multiple myeloma on a global basis. bb2121 and bb21217 both bind to BCMA, a cell surface protein expressed on cancer cells. Multiple myeloma is a hematologic malignancy that develops in the bone marrow in which normal antibody-producing plasma cells transform into myeloma. The growth of the cancer cells in the bone marrow blocks production of normal blood cells and antibodies, and also causes lesions that weaken the bone. BCMA is expressed on normal plasma cells, some mature B cells, and on malignant multiple myeloma cells, but is believed to be absent from other normal tissues.

#### *Collaboration with Celgene*

The bb2121 and bb21217 product candidates arose from our multi-year collaboration with Celgene. Since our collaboration arrangement with Celgene was announced in March 2013, we have worked collaboratively to discover, develop and commercialize CAR T cell product candidates in oncology. Our collaboration arrangement with Celgene was amended in June 2015 to focus on CAR T cell product candidates targeting BCMA. In March 2018, we entered into an agreement with Celgene to co-develop and co-promote bb2121 in the United States, in which both parties will share equally in costs and profits on terms described more fully below under “Strategic collaborations-Our strategic alliance with Celgene.” In September 2017, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb21217, and we retain an option to co-develop and co-commercialize this product candidate.

In January 2019, Celgene announced that it has entered into a definitive merger agreement under which Bristol-Myers Squibb Company, or BMS, will acquire Celgene, and that the transaction is expected to be completed in the third quarter of 2019. The acquisition of Celgene by BMS may result in organizational and personnel changes, shifts in business focus or other developments that may have a material adverse effect on our collaboration with Celgene. There is no guarantee that BMS will place the same emphasis on the collaboration or on the development and commercialization of the bb2121 or bb21217 product candidates.

#### *Development of the bb2121 and bb21217 product candidates*

In collaboration with Celgene, we are developing the bb2121 and bb21217 product candidates, with the goal for filing for regulatory approval in multiple myeloma on a global basis. The FDA and EMA have granted Orphan Drug status to both bb2121 and bb21217 product candidates for the treatment of patients with relapsed and refractory multiple myeloma. The FDA has granted Breakthrough Therapy designation and the EMA has granted PRIME eligibility to the bb2121 product candidate for relapsed and refractory multiple myeloma. We and Celgene anticipate a potential approval of the bb2121 product candidate for the treatment of relapsed and refractory multiple myeloma in the second half of 2020.

For the development of the bb2121 product candidate, Celgene is conducting, or is planning to conduct, the following clinical studies in multiple myeloma:

- CRB-401, an open label, single-arm, multicenter, phase 1 study of patients with relapsed and refractory multiple myeloma. In February 2016 we announced that the first patient had been treated in this study. The final patient in this study was treated in February 2018.
- KarMMA (MM-001), an open label, single-arm, multicenter, phase 2 study of patients with relapsed and refractory multiple myeloma. In February 2018, Celgene announced that the first patient had been treated in this registration-enabling study, and in November 2018, Celgene announced that enrollment for this study is complete.
- KarMMA-2 (MM-002), the planned multi-cohort, open-label, multicenter phase 2 study of patients with relapsed and refractory multiple myeloma and in high-risk multiple myeloma. Celgene has announced that it expects to initiate this study in 2019.
- KarMMA-3 (MM-003), the planned multicenter, randomized, open-label phase 3 study comparing the efficacy and safety of bb2121 versus standard triplet regimens in patients with relapsed and refractory multiple myeloma. Celgene has announced that it expects to initiate this study in 2019.
- A planned multicenter phase 2 study of patients with newly-diagnosed multiple myeloma. Celgene has announced that it expects to initiate this study in the second half of 2019.

For the development of the bb21217 product candidate, we are conducting the CRB-402 study, an open label, single-arm, multicenter, phase 1 study of patients with relapsed and refractory multiple myeloma. In September 2017, we announced that the first patient had been treated in this study.

#### *Clinical results of bb2121 and bb21217 product candidates*

- **The CRB-401 study - phase 1 study of bb2121 for the treatment of patients with relapsed and refractory multiple myeloma**

Our CRB-401 study is a single-dose, open-label, non-randomized, multi-site phase 1 dose escalation/ dose expansion clinical study in the United States to examine the safety and efficacy of our bb2121 product candidate in up to 50 patients with relapsed and refractory multiple myeloma. In order to be eligible for CRB-401, patients must have received three prior regimens, including a proteasome inhibitor (PI; bortezomib or carfilzomib) and an immunomodulatory agent (IMiD; lenalidomide or pomalidomide), or be “double-refractory” to both a proteasome inhibitor and an immunomodulatory agent. In the expansion cohort, patients must have received at least a PI, an IMiD and daratumumab, and be refractory to their last line of therapy. Patients receive one cycle of lymphodepletion with cyclophosphamide and fludarabine prior to infusion of the bb2121 drug product. In September 2017, we announced that the expansion cohort of the study had been initiated with first patient treated, and the final patient enrolled in this study was treated in February 2018.

The primary endpoint of the study is the incidence of adverse events and abnormal laboratory test results, including dose-limiting toxicities. The study also seeks to assess disease-specific response including: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. The study also seeks to determine the maximally tolerated dose and recommended dose for further clinical trials. Each patient is followed for up to 60 months post-treatment, and then is enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 60-month period.

In June 2018, we and Celgene presented updated clinical data from the CRB-401 study at the American Society of Clinical Oncology Annual Meeting, or ASCO. All data presented at ASCO and summarized below are as of the data cut-off date of March 29, 2018:

- 43 patients had been enrolled and treated in either the dose-escalation cohort of the study, at four dose levels (50 x 10<sup>6</sup>, 150 x 10<sup>6</sup>, 450 x 10<sup>6</sup> and 800 x 10<sup>6</sup> CAR T cells), or in the dose expansion cohort in a dose range between 150 and 450 x 10<sup>6</sup> CAR T cells. Patients in the study were heavily pre-treated, with a median of seven prior myeloma treatment regimens (with a range of 3 to 14) in the dose escalation cohort (n=21), and with a median of eight prior regimens (with a range of 3 to 23) in the dose expansion cohort (n=22). Approximately 90% of the patients had received prior treatment with two IMiD therapies, two proteasome inhibitors, daratumumab and an autologous stem cell transplant.

- Response outcomes in patients evaluable for efficacy, with at least 2 months of response data or progressive disease/ death within 2 months were as follows:

CAR T cell dose level	50 x 10 <sup>6</sup>	150 x 10 <sup>6</sup>	> 150 x 10 <sup>6</sup>
N	3	14	22
Median follow up (min, max)	84 days (59, 94)	87 days (36, 638)	194 days (46, 556)
<u>Measures:</u>			
Overall response rate (ORR)	33.3%	57.1%	95.5%
Complete response (CR)	0%	42.9%	50%
Very good partial response (VGPR)	0%	7.1%	36.4%
Median duration of response (mDOR)	1.9 months	Not estimable	10.8 months

- Responses were dose-related and observed for both low and high BCMA expression levels. In patients treated with 450 x 10<sup>6</sup> CAR T cells whose myeloma cells expressed low levels of BCMA (0 to 50% of cells BCMA positive), 8 of 8 had a response. In those expressing high BCMA ( $\geq$ 50% BCMA positive), 10 of 11 had a response.
- The median progression-free survival (PFS) estimate for patients in the dose-escalation phase treated at active doses ( $\geq$ 150 x 10<sup>6</sup> CAR T cells) was 11.8 months (95% CI 8.8, NE), while patients receiving 50 x 10<sup>6</sup> CAR T cells had a median PFS of 2.7 months (95% CI 1.0, 2.9).
- In the dose-escalation and expansion phase of the study, all patients who responded and were evaluable for minimal residual disease (MRD as measured by adaptive next-generation sequencing assay) (n=16) were MRD negative at one or more time points. Additionally, two patients who did not have a response and were evaluated for MRD were MRD positive at month one. The median PFS estimate in MRD negative responders (n=16) was 17.7 months (95% CI: 5.8, NE).
- Among all infused patients (n=43), 63% had cytokine release syndrome (CRS), mostly Grade 1 & 2, with 2 patients experiencing Grade 3 CRS (5%). Nine patients (21%) received tocilizumab, including 4 patients (9%) who also received steroids and the median duration of CRS was 6 days (1, 32). For patients receiving 150 x 10<sup>6</sup> CAR T cells (n=18), the rate of CRS was 39% with no grade 3 cases. For patients receiving  $\geq$ 150 x 10<sup>6</sup> CAR T cells (n=22), the rate of CRS was 82% with 9.1% of patients experiencing grade 3 events. Also among all infused patients, there were 14 patients (33%) who experienced neurotoxicity, with one patient experiencing a grade 3 or higher event. Other frequent Grade 3/4 AEs included cytopenias commonly associated with lymphodepleting chemotherapy such as neutropenia (79%), thrombocytopenia (51%) and anemia (44%), as well as infection (any grade) with a frequency of 61% overall and 23% in the first month. Grade 3 or higher infection occurred with a frequency of 21% overall and 5% in the first month.

- **The CRB-402 study - phase 1 clinical study of bb21217 for the treatment of patients with relapsed and refractory multiple myeloma**

Our CRB-402 study is a single-dose, open-label, non-randomized, multi-site phase 1 dose escalation/ dose expansion clinical study in the United States to examine the safety and efficacy of our bb21217 product candidate in up to 50 patients with relapsed and refractory multiple myeloma. In order to be eligible for CRB-402, patients must have received three prior regimens, including a proteasome inhibitor (PI: bortezomib or carfilzomib) and immunomodulatory agent (IMiD: lenalidomide or pomalidomide), or be “double-refractory” to both a proteasome inhibitor and an immunomodulatory agent. In the expansion cohort, patients must have received at least a PI, and IMiD and daratumumab, and be refractory to their last line of therapy. Patients receive one cycle of lymphodepletion with cyclophosphamide and fludarabine prior to infusion of the bb21217 drug product. In September 2017, we announced the treatment of the first patient with relapsed and refractory multiple myeloma in this study.

The primary endpoint of the study is the incidence of adverse events and abnormal laboratory test results, including dose-limiting toxicities. The study also seeks to assess disease-specific response including: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. The study also seeks to determine the maximally tolerated dose and recommended dose for further clinical trials. Each patient will be followed for up to 60 months post-treatment, and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 60-month period.

In December 2018, we and Celgene presented clinical data from the CRB-402 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date of October 18, 2018:

- 12 patients had been enrolled and treated in the dose-escalation cohort of the study, all at the 150 x 10<sup>6</sup> CAR T cells dose level. Patients had a median age of 63 years (with a range of 44 to 69 years). They had received a median of seven prior lines of therapy (with a range of 4 to 17 lines) and 83 percent of patients received a prior autologous stem cell transplant. Fifty-eight percent (n=7) of patients had high-risk cytogenetics.
- The median follow-up after treatment was 26 weeks (with a range of 4 to 51 weeks). The primary endpoint is safety measured by frequency of adverse events (AEs), dose limiting toxicity (DLT) and changes in laboratory results. Secondary endpoints include disease specific response criteria based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.
- Of the 12 patients who received treatment with bb21217, 83 percent (n=10) achieved an objective clinical response by IMWG criteria. As of the data extract, responses are ongoing in nine of 10 patients, including three with a complete response (CR) or stringent complete response (sCR), two with a very good partial response (VGPR) and four with a partial response (PR).
- Evidence of myeloma in the bone marrow, known as minimal residual disease (MRD), was undetectable at a minimum of two time points, by next-generation sequencing at a sensitivity level of 10-5 or better in all responders who had evaluable bone marrow samples (n=4) with some as early as day 15.
- CAR T cell expansion was observed during the first 30 days following treatment in all evaluable patients (n=11) with anti-BCMA CAR T cells showing sustained persistence in all patients (3/3) with six or more months of follow-up.
- The safety results were manageable and consistent with known toxicities of CAR T therapies. Eight of the 12 patients (67 percent) treated with bb21217 developed cytokine release syndrome (CRS); four Grade 1, three Grade 2, one Grade 3 case and no Grade 4 cases. Additionally, three of the 12 patients (25 percent) experienced neurotoxicity, including one Grade 1, one Grade 2 and one Grade 4 case. All CRS and neurotoxicity events resolved and no deaths occurred on study. Following the Grade 4 neurotoxicity event, patients were divided into two groups based on tumor burden and dosing continued at 150 x 10<sup>6</sup> CAR T cells for a total of 12 patients treated at this dose level.

#### **Our other preclinical research opportunities in cancer**

We are pursuing multiple programs that leverage the unique properties of lentiviral vectors to target T cells as a therapy for various cancers. This represents a direct application of our expertise in gene therapy and our capabilities, know-how and patents associated with lentiviral gene therapy and gene editing for *ex vivo* applications. We have programs at various stages of research and preclinical development through our collaborations with Regeneron, Medigene AG, Gritstone Oncology, Inc., and TC Biopharm Limited against a variety of targets relevant to both hematologic and solid tumors. We also have academic collaborations at various stages of research and preclinical development at the University of North Carolina and the Fred Hutchinson Cancer Research Center. We are also independently researching and developing other CAR T cell product candidates against a variety of cancer targets.

## **Our Gene Editing Capabilities**

In June 2014, we acquired Pregenex, a privately-held biotechnology company headquartered in Seattle, Washington. Through the acquisition, we obtained rights to Pregenex's gene editing technology platform and cell signaling technology. Since the acquisition, we have integrated these technologies and research team and we have expanded the scope of our research efforts in this area. We are focused on utilizing homing endonuclease and megaTAL gene editing technologies in a variety of potential applications and disease areas, including for oncology and hematology. Homing endonucleases and megaTALS are novel enzymes that provide a highly specific and efficient way to modify the genome of a target cell to potentially treat a variety of diseases.

All of the gene-editing technologies currently being explored by the pharmaceutical industry, including zinc finger nucleases, CRISPR/Cas9, and TALENs, share common features of a DNA binding domain and a DNA cleavage domain. They all differ in specificity, size, ease of delivery and as naturally occurring versus engineered nucleases. Homing endonucleases and megaTALS are based on a naturally-occurring class of DNA cleaving enzymes that function as monomeric proteins able to bind DNA in a sequence-specific manner and cleave their target site. We believe there are multiple advantages of homing endonucleases and megaTALS compared to other gene editing technologies, most notably: they are highly specific and efficient in cutting DNA and their compact size simplifies delivery to therapeutically relevant cell types. We are using our gene editing platform, along with collaborations with multiple academic institutions, to potentially discover and develop next generation versions of our current *ex vivo* gene therapy product candidates, and to potentially expand into new disease indications.

## **Manufacturing**

Our gene therapy platform has two main components: lentiviral vector production and the target cell transduction process, which results in drug product.

### ***Our lentiviral manufacturing process***

Our lentiviral vectors are assembled using a human cell line called HEK293T. The HEK293T cells are maintained in disposable flasks until sufficient cell mass has been generated to fill approximately 40 ten tray cell factories, or TTCFs, then transferred and allowed to adhere to the bottom of the trays. Adherent cells are transfected with multiple plasmids encoding all the genetic material required to assemble the lentiviral vector carrying the functional gene of interest. The transfected HEK293T cells then assemble our lentiviral vectors packaged with the functional gene of interest, which bud off into the cell culture media. The media containing the assembled vectors is harvested, purified, concentrated and formulated prior to freezing for storage. These finished lentiviral vectors are what is ultimately used to transduce the targeted cells isolated from the patient.

We believe that our lentiviral vectors have broad applicability, since the majority of the viral production system can remain the same, while we change only the therapeutic gene "cassette" depending on the disease. In other words, the vector "backbone" stays the same, while only the therapeutic gene and related sequences are changed. If we were to undertake drug development in an additional indication, we believe we could rapidly move forward using this lentiviral vector backbone and associated assays, simply by switching the therapeutic gene insert and associated control elements.

Although we intend to continue manufacturing our Lenti-D vectors in TTCFs, we are adapting our LentiGlobin, bb2121 and bb21217 vector production technology to scalable production systems with the potential to satisfy an increased number of patients per manufacturing cycle, and we have demonstrated successful production of our LentiGlobin, bb2121 and bb21217 vectors at the scale we believe will support potential commercial demand. We intend to use a mix of internal and third-party manufacturing capabilities to accommodate future demand for our drug candidates, if approved, in their current indications as well as those beyond our initial focus.

### ***Our HSC transduction process in severe genetic disease***

In severe genetic disease, the ultimate product of our manufacturing processes is the patient's own gene-modified HSC cells, which we refer to as our drug product. The process for producing drug product for our HSC-based product candidates is as follows:

1. **Selection:** We extract HSCs from peripheral blood mononuclear cells obtained from the patient's blood by apheresis following mobilization via a colony stimulating factor (or previously in SCD, by bone marrow harvest). The process is carried out using existing hospital infrastructure and standard protocols currently in place for stem cell transplant procedures, with enhanced controls for extracting the cells to be used for making our drug product.
2. **Pre-stimulation:** The isolated HSCs are treated with a mixture of growth factors that help enable an efficient transduction process.

3. **Transduction:** The isolated, purified and pre-treated HSCs are exposed to our lentiviral vectors containing the appropriate functional gene and additional proprietary elements for a period of time to facilitate transduction and insertion of the therapeutic DNA into the genome of the target cells.
4. **Final harvest:** Once transduction is complete, the gene-modified HSCs are washed and re-suspended into cell culture media to remove any residual impurities. A portion of the harvested cells is removed for quality control release testing, which includes ensuring that transduction was successful and the functional gene delivered by the vector is adequately expressed by the target cells.
5. **Formulation and freeze:** The remaining cells are appropriately formulated and cryopreserved.

The final step is to return the gene-modified HSCs to the patient.

#### ***Our T cell transduction process in cancer***

In cancer, the ultimate product of our manufacturing processes is the patient's own gene-modified T cells, which we refer to as our drug product. The process for producing drug product for our T cell-based product candidates is as follows:

1. **Leukapheresis:** We collect white blood cells from the patient's blood through a process called leukapheresis. The process is carried out using existing hospital infrastructure and standard protocols currently in place for blood donation procedures, with enhanced controls for extracting the cells to be used for making our drug product.
2. **Activation:** The white blood cell mixture, which includes T cells, is treated with proprietary processes to enable an efficient transduction process.
3. **Transduction:** The isolated, purified and pre-treated T cells are exposed to our lentiviral vectors containing the appropriate functional gene for a period of time to facilitate transduction and insertion of the therapeutic DNA into the genome of the target cells.
4. **Expansion:** The transduced T cells are then expanded for a period of approximately one week to increase the number of gene-modified T cells.
5. **Final harvest:** The gene-modified T cells are washed and re-suspended into cell culture media to remove any residual impurities. A portion of the harvested cells is removed for quality control release testing, which includes ensuring that transduction was successful and the functional gene delivered by the vector is adequately expressed by the target cells.
6. **Formulation and freeze:** The remaining cells are appropriately formulated and cryopreserved.

The final step is to return the gene-modified T cells to the patient.

#### **Manufacturing Arrangements**

In November 2017, we purchased a partially completed manufacturing facility located in Durham, North Carolina for \$11.5 million. We acquired this 125,000 square foot facility to provide manufacturing capacity for our lentiviral vectors in support of our current and planned gene and cell therapy product candidates. We currently expect that our facility will begin to produce lentiviral vector in 2021. We have also entered into multi-year agreements with external manufacturing partners in the United States and Europe (Brammer Bio, Novasep and SAFC Carlsbad, Inc., or SAFC, a subsidiary of MilliporeSigma), which are partnering with us on production of lentiviral vector across all of our programs. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. and apceth Biopharma, or apceth, to produce drug product for Lenti-D, LentiGlobin and bb21217. Currently, SAFC is the sole manufacturer of the lentiviral vector and apceth is the sole manufacturer of the drug product to support our potential commercial launch of LentiGlobin in Europe for the treatment of TDT. In our manufacturing agreement with SAFC, we are required to provide rolling forecasts for products on a quarterly basis, a portion of which will be considered a binding, firm order, subject to a purchase commitment. In our manufacturing agreement with apceth, we reserve production capacity for the manufacture of our drug product. In January 2019, apceth announced that it has entered into an agreement to be acquired by Hitachi Chemical Co. Ltd., in a transaction expected to close in April 2019. Celgene manufactures drug product for bb2121. We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions and potential commercial launch. We are engaging in negotiations with apheresis centers that will be the centers for collection of HSCs from the patient and for infusion of drug product to the patient. For the treatment of patients with our drug product in the commercial setting, we intend to partner with participating apheresis centers, which we refer to as qualified treatment centers. In anticipation of the potential regulatory approval of LentiGlobin in Europe, we expect to first engage qualified treatment centers in Germany, Italy, and the United Kingdom in 2019.

## **Commercial Operations**

Subject to approval from the EMA of our LentiGlobin product candidate for the treatment of adult and adolescent patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes, we expect to launch LentiGlobin in various jurisdictions in Europe in 2019. As we plan our potential transition into a commercial-stage company, we have started to build commercial operations in the United States and Europe with a goal of delivering LentiGlobin to patients through qualified treatment centers. In the course of preparing for a potential commercial launch in 2019, we have begun a staged build of commercial capabilities by adding employees with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. We expect to continue expansion of these capabilities throughout 2019 and beyond as we continue to implement appropriate quality systems, compliance policies, systems and procedures, as well as internal systems and infrastructure in order to support our complex supply chain, qualify and train treatment centers, establish patient-focused programs, educate healthcare professionals, and secure reimbursement. The timing and conduct of these commercial activities will be dependent upon regulatory approvals and on agreements we have made or may make in the future with strategic collaborators. As part of the commercialization process, we are engaged in discussions with stakeholders across the healthcare system, including public and private payors, patient advocates and organizations, professional societies, and healthcare providers, to explore new payment models that we hope will enable access to more patients. Ultimately, we intend to utilize the commercial infrastructure that we build to support the potential for multiple product launches sequentially across multiple geographies. For many territories and countries, we may also elect to utilize strategic partners, distributors, or contract field-based teams to assist in the commercialization of our products.

## **Strategic Collaborations**

Our objective is to develop and commercialize products based on the transformative potential of gene therapy to treat patients with severe genetic diseases and cancer. To access the substantial funding and other resources required to develop and commercialize gene therapy products in these diseases, we have formed, and intend to seek other opportunities to form, strategic collaborations with third parties who can augment our industry leading gene therapy, T cell immunotherapy, lentiviral vector and gene-editing expertise. To date, we have focused on forging a limited number of significant strategic collaborations with leading pharmaceutical companies and academic research centers where both parties contribute expertise to enable the discovery and development of potential product candidates.

Our strategic collaborations include relationships with:

- Celgene, in the development of the bb2121 and bb21217 product candidates in multiple myeloma;
- Regeneron, in the discovery, development, and commercialization of novel cell therapies for cancer;
- Medigene AG, to discover TCR product candidates in the field of cancer;
- Gritstone Oncology, Inc., to validate targets and discover TCR product candidates in the field of cancer; and
- TC BioPharm Limited, in the research and development of gamma delta CAR T cells directed at hematologic and solid tumor targets.

## ***Our collaboration with Celgene***

In March 2013, we announced a strategic collaboration with Celgene to discover, develop and commercialize chimeric antigen receptor-modified T cells, or CAR T cells, as potentially disease-altering gene therapies in oncology, which was amended and restated in June 2015, and amended again in February 2016 and in September 2017. The multi-year research and development collaboration focused on applying our expertise in gene therapy technology to CAR T cell-based therapies, to target and destroy cancer cells. The research collaboration term ended in June 2018, with the bb2121 and bb21217 product candidates arising from the collaboration.

In February 2016, Celgene exercised its option with respect to the bb2121 product candidate, and we exclusively licensed to Celgene the worldwide rights to develop and commercialize the bb2121 product candidate, while retaining an option to co-develop and co-promote the bb2121 product candidate in the United States. In connection with its exercise of its option to obtain an exclusive license, Celgene paid to us an option fee in the amount of \$10.0 million. In March 2018, we exercised our option to co-develop and co-promote the bb2121 product candidate in the United States. Under the terms of the co-development and co-promotion agreement that we have with Celgene for the development and commercialization of bb2121, we share equally in all costs relating to developing, commercializing and manufacturing the product candidate within the United States and we would share equally in the United States profits. We are also entitled to receive up to \$10.0 million in clinical milestone payments and outside of the United States, up to \$54.0 million in regulatory milestone payments and up to \$36.0 million in commercial milestone payments. In addition, to the extent that bb2121 is commercialized, we are entitled to receive tiered royalty payments ranging from the mid-single digits to low-teens based on a percentage of net sales generated outside of the United States. The royalties payable to us are subject to certain reductions, including any royalty payments required to be made by Celgene to acquire patent rights, with an aggregate minimum floor.

Effective as of September 2017, Celgene has exercised its option with respect to the bb2121 product candidate, and we have exclusively licensed to Celgene the worldwide rights to develop and commercialize the bb2121 product candidate, while retaining an option to co-develop and co-promote the bb2121 product candidate in the United States on terms substantially similar to the co-development and co-promotion arrangement for the bb2121 product candidate. In connection with its exercise of its option to obtain an exclusive license, Celgene paid to us an option fee in the amount of \$15.0 million. Under the terms of the license agreement with Celgene for the exclusive rights to the development and commercialization of bb2121, we are and will be responsible for conducting and funding all research and development activities performed up through completion of the CRB-402 study. Celgene has agreed to reimburse us a specified amount per patient in the event we and Celgene mutually agree to expand the trial beyond a specified number of patients per clinical trial. In addition, if we do not exercise our option to co-develop and co-promote the bb2121 product candidate in the United States, we will also be eligible to receive up to \$10.0 million in clinical milestone payments, up to \$117.0 million in regulatory milestone payments and up to \$78.0 million in commercial milestone payments, as well as a percentage of net sales as a royalty in a range from the mid-single digits to low-teens. The royalties payable to us are subject to certain reductions, including for any royalty payments required to be made by Celgene to acquire patent rights, with an aggregate minimum floor. Celgene will assume certain development obligations and must report on their progress in achieving these milestones on a quarterly basis.

Our collaboration with Celgene is governed by a joint governance committee, or JGC, formed by representatives from us and Celgene. The JGC, among other activities, reviews and approves development and commercialization plans and budgets for activities in the United States. The parties share responsibility for the manufacture and supply of the bb2121 product candidate and, if we exercise our option to co-develop and co-promote, of the bb2121 product candidate. Prior to the exercise of our option to co-develop and co-promote the bb2121 product candidate, Celgene is solely responsible for all costs and expenses of manufacturing and supplying the bb2121 product candidate beyond the requirements for conducting the CRB-402 study. Subject to customary "back-up" supply rights granted to Celgene, we have the sole right to manufacture or have manufactured supplies of vectors and associated payloads manufactured for incorporation into the optioned product candidates. Celgene will reimburse us for our costs to manufacture and supply such vectors and associated payloads, plus a mark-up.

We received an initial up-front payment of \$75.0 million from Celgene in connection with the collaboration, plus an additional \$25.0 million in connection with the amendment in June 2015. Either party may terminate the agreements upon written notice to the other party in the event of the other party's uncured material breach. Celgene may terminate the agreement for any reason upon prior written notice to us. If the agreements are terminated, rights to product candidates in development at the time of such termination will be allocated to the parties through a mechanism included in the agreements. In addition, if Celgene has the right to terminate any co-development and co-promotion agreement or license agreement for our breach, Celgene may elect to continue such agreement however, any amounts payable by Celgene to us under such agreement will be reduced.

In January 2019, Celgene announced that it has entered into a definitive merger agreement under which BMS will acquire Celgene, and that the transaction is expected to be completed in the third quarter of 2019. The acquisition of Celgene by BMS may result in organizational and personnel changes, shifts in business focus or other developments that may have a material adverse effect on our collaboration with Celgene. There is no guarantee that BMS will place the same emphasis on the collaboration or on the development and commercialization of the bb2121 or bb21217 product candidates.

#### **Intellectual property**

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have developed or in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of gene therapy products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, certain genes, transgenes, methods of transferring genetic material into cells, genetically modified cells, processes to manufacture our lentivirus-based product candidates and other proprietary technologies and processes related to our lead product development candidates. As of January 31, 2019, our patent portfolio includes the following:

- approximately 235 patents or patent applications that we own or have exclusively in-licensed from third parties related to lentiviral vectors and vector systems;
- approximately 34 patents or patent applications that we have non-exclusively in-licensed from third parties related to lentiviral vectors and vector systems;
- approximately 53 patents or patent applications that we own or have exclusively in-licensed from third parties, including eight that are co-owned with MIT, related to vector manufacturing or production;
- approximately 104 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to therapeutic cellular product candidates;
- approximately 324 patents or patent applications that we own or have exclusively in-licensed or optioned from third parties related to oncology product candidates, including CAR T cell vector systems and manufacturing, T cell manufacturing, and therapeutic T cells;
- approximately 142 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to gene editing compositions and methods; and
- approximately 44 patent applications that we have non-exclusively in-licensed from third parties related to gene editing compositions and methods.

Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our gene therapy product candidates manufacturing processes. Examples of the products and technology areas covered by our intellectual property portfolio are described below. See also “License agreements.” From time to time, we also evaluate opportunities to sublicense our portfolio of patents and patent applications that we own or exclusively license, and we may enter into such licenses from time to time.

#### *β-thalassemia/SCD*

The β-thalassemia/SCD program includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio contains patent applications directed to FLAP/cPPT elements and lentiviral vectors utilized to produce our LentiGlobin product candidate for β-thalassemia and SCD. As of January 31, 2019, we had an exclusive license to ten issued U.S. patents and one pending U.S. patent application. Corresponding foreign patents include issued patents in Australia, Canada, China, Europe, Hong Kong, Israel, and Japan. We expect the issued composition of matter patents to expire from 2019-2023 in the United States, and from 2019-2020 in the rest of the world (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2019-2020 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2019-2020 (worldwide, excluding possible patent term extensions).
- **RDF.** The in-licensed patent portfolio from Research Development Foundation, or RDF, in part, contains patents and patent applications directed to aspects of our lentiviral vectors utilized to produce our LentiGlobin product candidate for β-thalassemia and SCD. As of January 31, 2019, we had an exclusive license (from RDF) to eight issued U.S. patents related to our lentiviral vector platform. Corresponding foreign patents and patent applications related to our lentiviral vector platform include pending applications or issued patents in Canada, Europe, and Israel. We expect the issued composition of matter patents to expire from 2021-2027 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).

- **MIT/bluebird bio.** This co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral β-globin expression vectors. As of January 31, 2019, we co-owned three issued U.S. patents and one pending U.S. patent application, as well as corresponding foreign patents issued in Europe and Hong Kong. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2023 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2023 (worldwide, excluding possible patent term extensions). We note that we have an exclusive license to MIT's interest in this co-owned intellectual property.
- **Children's Medical Center Corporation (CMCC)/bluebird bio.** This co-owned patent portfolio contains patent applications directed to certain specific compositions of matter for treating β-thalassemia/SCD. As of January 31, 2019, we co-owned one pending PCT application. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We note that we have an option to exclusively license CMCC's interest in this co-owned intellectual property.

Our β-thalassemia/SCD research program also includes the additional patent portfolio described below.

- **β-thalassemia/SCD Product Candidate Licenses.** We have in-licensed patents and patent applications that are directed to certain specific compositions of matter and methods for treating β-thalassemia/SCD. As of January 31, 2019, we had an exclusive license to two pending U.S. patent applications and 24 pending corresponding foreign applications. We expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2019, we had a non-exclusive license to three issued U.S. patents, one pending U.S. patent application, and ten pending corresponding foreign patent applications and 19 issued foreign patents. We expect the issued composition of matter and method patents to expire in 2029 in the United States and in the rest of the world (excluding possible patent term extensions). We expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2029 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2029 (worldwide, excluding possible patent term extensions).

#### *Cerebral Adrenoleukodystrophy (CALD)*

The CALD program includes the following patent portfolios described below.

- **Pasteur Institute.** The in-licensed Pasteur patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our Lenti-D product candidate for CALD.
- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our Lenti-D product candidate for CALD.
- **bluebird bio.** The bluebird bio patent portfolio contains patent applications directed to compositions of matter for CALD gene therapy vectors and compositions and methods of using the vectors and compositions in cell-based gene therapy of adrenoleukodystrophy or adrenomyeloneuropathy. As of January 31, 2019, we owned three U.S. patents and five pending corresponding foreign applications and 26 issued foreign patents. We expect the issued composition of matter patents for CALD gene therapy vectors to expire in 2032 (excluding possible patent term extensions). Further, we expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions).

### ***Multiple Myeloma***

The multiple myeloma program includes the following patent portfolios described below.

- **Pasteur Institute.** The in-licensed Pasteur patent portfolio contains patents and patent applications described above that are directed towards aspects of our lentiviral vectors utilized to produce our bb2121 product candidate for multiple myeloma.
- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our bb2121 product candidate for multiple myeloma. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2019, we had an exclusive license (from RDF) to four issued patents and two pending U.S. patent applications related to our oncology platform. We expect the issued patent to expire in 2021-2022 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).
- **Biogen.** The in-licensed patent portfolio from Biogen Inc., formerly Biogen Idec MA Inc. and referred to herein as Biogen, contains patents and patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2019, we had a co-exclusive license to nine issued U.S. patents and two pending U.S. patent applications and five pending corresponding foreign applications and 113 issued corresponding foreign patents related to bb2121. We expect the issued patents to expire from 2020-2032 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2020-2032 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2020-2032 (worldwide, excluding possible patent term extensions).
- **NIH.** The in-licensed patent portfolio from NIH contains patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2019, we had an exclusive license to one issued U.S. Patent, one pending U.S. patent application and 19 corresponding foreign patent applications and six issued corresponding foreign patents related to bb2121. We expect the issued composition of matter patents to expire in 2033-2034 (excluding possible patent term extensions). We expect any other composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).
- **bluebird bio.** The bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells. As of January 31, 2019, we owned six pending U.S. patent applications, 96 corresponding foreign patent applications, 3 foreign patents and one pending PCT application. We expect the issued composition of matter and methods patents to expire in 2035 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2035-2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035-2038 (worldwide, excluding possible patent term extensions).

### ***Lentiviral platform (e.g., vectors, manufacturing, and cell therapy products)***

The lentiviral platform, which is potentially applicable to the β-thalassemia, SCD, CALD, oncology and other potential programs, includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio contains the patents and patent applications described above.
- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above.
- **SIRION.** The in-licensed patent portfolio from SIRION Biotech GmbH, or SIRION, contains patents directed to methods of manufacturing *ex vivo* gene therapy products with a lentiviral vector. As of January 31, 2019, we had an exclusive license to one issued U.S. Patent, one pending U.S. patent application and two corresponding foreign patent applications and one issued corresponding foreign patent. We expect the issued method patents to expire in 2033 (excluding possible patent term extensions). We expect any other composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- **bluebird bio.** Another component of the bluebird bio patent portfolio includes the vector manufacturing platform and is potentially applicable to the CALD, β-thalassemia, SCD, oncology, and other programs. This portion of the portfolio contains patents and patent applications directed to improved methods for transfection and transduction of therapeutic cells. As of January 31, 2019, we owned one issued U.S. patent, three pending U.S. patent applications and 44 corresponding foreign patent applications and 21 issued corresponding foreign patents. We expect the issued method patents to expire in 2032 (excluding possible patent term extensions). We expect composition of matter and method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2032-2037 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032-2037 (worldwide, excluding possible patent term extensions).

**Oncology platform (e.g., vectors, manufacturing, and T cell-based products)**

Our T cell-based oncology platform and oncology research program, which is applicable to our multiple myeloma program and other potential programs in cancer, includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio contains the patents and patent applications described above.
- **RDF.** The in-licensed RDF patent portfolio described above contains patents and patent applications that are also applicable to our oncology platform. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2019, we had an exclusive license (from RDF) to four issued patents and two pending U.S. patent applications related to our oncology platform. We expect the issued patents to expire in 2021-2022 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2021-2022 (worldwide, excluding possible patent term extensions).
- **bluebird bio.** One aspect of the bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells directed against various cancers and improved CAR T cell compositions. As of January 31, 2019, we owned one issued U.S. patent, five pending U.S. patent applications and 29 corresponding foreign patent applications; six families of pending U.S. provisional applications; and four pending PCT applications. We expect the issued composition of matter patent to expire in 2034 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033-2037 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2033-2037 (worldwide, excluding possible patent term extensions).
- **T Cell Manufacturing Methods License.** We have in-licensed patents and patent applications that are directed to certain specific methods for generating CAR T cells. As of January 31, 2019, we had a nonexclusive license to two issued U.S. patents, one pending U.S. patent application, and 30 corresponding issued foreign patents. We expect the issued method patents to expire in 2026 (excluding possible patent term extensions). Further, we expect methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2026 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2026 (worldwide, excluding possible patent term extensions).
- **T Cell Immunotherapy Product Candidate Licenses.** We have in-licensed patents and patent applications that are directed to certain specific compositions of matter for generating CAR T cells directed against various cancers and related methods of treatment. As of January 31, 2019, we have an exclusive license to one issued U.S. patent and ten corresponding foreign patents and co-own a pending US application and seven corresponding foreign patent applications to a particular target antigen. We expect the issued composition of matter patent to expire in 2025 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2036 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2019, we have an exclusive license to three issued U.S. patents, three corresponding foreign patents, and one corresponding foreign patent application to another particular target antigen. We expect the issued method of use patents to expire in 2029 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2029 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2029 (worldwide, excluding possible patent term extensions).

***Gene editing platform (e.g., homing endonucleases, chimeric endonucleases, megaTALs, genetically modified cells)***

The gene editing platform includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.
- **RDF.** The in-licensed RDF patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.
- **Gene Editing License.** We in-licensed patent portfolios that contain patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our β-thalassemia, SCD, oncology and other programs. As of January 31, 2019, we had an exclusive/co-exclusive license to six issued U.S. patents and one pending U.S. patent application and 29 corresponding foreign patents and six corresponding patent applications related to our gene editing platform. We expect the issued composition of matter patents to expire in 2030 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2030 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2030 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2019, we had an exclusive license to two issued U.S. patents and six corresponding foreign patents related to our gene editing platform. We expect the issued composition of matter patent to expire in 2031 in the United States (excluding possible patent term extensions) and in 2027 in the rest of the world. Further, we expect composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2027 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2027 (worldwide, excluding possible patent term extensions).
- **Academic Gene Editing Licenses.** We in-licensed patent portfolios from multiple academic medical centers, each portfolio containing patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our β-thalassemia, SCD, oncology and other programs. As of January 31, 2019, we had an exclusive license to one issued U.S. patent and eight pending U.S. patent applications and five corresponding foreign patents and three corresponding patent applications related to our gene editing platform. We expect the issued patent to expire in 2032 (excluding possible patent term extensions) in the U.S. and 2027-3032 in the rest of the world. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2027-2032 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2027-2032 (worldwide, excluding possible patent term extensions). As of January 31, 2019, we also had a non-exclusive license to one issued U.S. patent application and two pending U.S. patent application related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2019, we had an exclusive license to two pending U.S. applications and 17 corresponding issued foreign patents and 18 corresponding foreign patent applications related to our gene editing platform. We expect the issued composition of matter patents to expire in 2033 (excluding possible patent term extensions). We expect other composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2031-2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2031-2033 (worldwide, excluding possible patent term extensions). As of January 31, 2019, we also had a non-exclusive license to one issued U.S. patent, one pending U.S. application, 21 corresponding foreign patent applications, and 18 corresponding foreign patents related to our gene editing platform. We expect the issued composition of matter patents to expire in 2033 (excluding possible patent term extensions). Further, we expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- **bluebird bio.** One aspect of the bluebird bio patent portfolio contains patent applications that are potentially applicable to certain aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our oncology and other programs. As of January 31, 2019, we owned one pending U.S. patent application and five corresponding foreign patent applications related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2037 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2037 (worldwide, excluding possible patent term extensions). As of January 31, 2019, we owned 11 families of PCT applications related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2037-2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2037-2038 (worldwide, excluding possible patent term extensions). As of January 31, 2019, we also owned two families of provisional applications related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). As of January 31, 2019, we co-owned (with Cellectis SA) two issued U.S. patents, eight corresponding foreign patent applications, and 10 corresponding foreign patents related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2034(excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2034 (worldwide, excluding possible patent term extensions).

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and third parties. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

#### **License agreements**

##### ***Inserm-Transfert***

In May 2009, we entered into an exclusive license with Inserm-Transfert, which is a wholly-owned subsidiary of Institut national de la santé et de la recherche médicale, for use of certain patents and know-how related to the ABCD1 gene and corresponding protein, for use in the field of human ALD therapy. Inserm-Transfert is referred to herein as Inserm. The last patent in the Inserm licensed patent portfolio expired in February of 2016. Inserm retains the right to practice the intellectual property licensed under the agreement for educational, clinical and preclinical studies purposes.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our Lenti-D product candidate, we will be obligated to pay Inserm a percentage of net sales as a royalty for the longer of the life of any patents covering the product or 10 years from first commercial sale. This royalty is in the low single digits. The royalties payable to Inserm are subject to reduction for any third party payments required to be made, with a minimum floor in the low single digits.

We are required to use all commercially reasonable efforts to develop licensed products and introduce them into the commercial market as soon as practical, consistent with our reasonable business practices and judgment in compliance with an agreed upon development plan. We have assumed certain development, regulatory and commercial milestone obligations and must report on our progress in achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement at any time. Either party may terminate the agreement in the event of the other party's material breach which remains uncured after 60 days of receiving written notice of such breach or in the event the other party becomes the subject of a voluntary or involuntary petition in bankruptcy and such petition is not dismissed with prejudice within 120 days after filing. In addition, Inserm may terminate the license agreement in the event that we cannot prove within 60 days of written notice from Inserm that we have been diligent in developing the licensed products and introducing them into the commercial market.

Absent early termination, the agreement will automatically terminate upon the expiration of all issued patents and filed patent applications within the patent rights covered by the agreement or 10 years from the date of first commercial sale of a licensed product, whichever is later. The license grant ceases in connection with any such termination. The longest lived patent rights licensed to us under the agreement expired in 2016.

#### ***Institut Pasteur***

We have entered into a license with Institut Pasteur for certain patents relating to the use of DNA sequences, lentiviral vectors and recombinant cells in the field of *ex vivo* gene therapy and CAR T cell-based therapy in a range of indications, excluding vaccinations. This agreement was amended twice in 2012, again in 2013 and most recently in 2015. The Institut Pasteur licensed patent portfolio includes at least 107 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration dates between 2019 and 2023. The license is exclusive for products containing human and non-human lentiviral vectors. Institut Pasteur retains the right, on behalf of itself, its licensees and research partners, to conduct research using the licensed intellectual property.

We have the right to grant sublicenses outright to third parties under the agreement. For the first sublicense including a product targeting β-hemoglobinopathies (including TDT and SCD) or ALD (including CALD and AMN), we must pay Institut Pasteur an additional payment of €3.0 million. If we receive any income (cash or non-cash) in connection with sublicenses for products targeting indications other than β-hemoglobinopathies (including TDT and SCD) or ALD (including CALD and AMN), we must pay Institut Pasteur a percentage of such income varying from low single digits if the sublicense also includes licenses to intellectual property controlled by us, and a percentage of sublicense income in the mid-range double digits if the sublicense does not include licenses to intellectual property controlled by us.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin, Lenti-D, bb2121 and bb21217 product candidates, we will be obligated to pay Institut Pasteur a percentage of net sales as a royalty. This royalty varies depending on the indication of the product but in any event is in the low single digits. In addition, starting in 2016 we must make under this agreement an annual maintenance payment which is creditable against royalty payments on a year-by-year basis. If the combined royalties we would be required to pay to Institut Pasteur and third parties is higher than a pre-specified percentage, we may ask Institut Pasteur to re-negotiate our royalty rates under this relationship.

We are required to use all reasonable commercial efforts (as compared to a company of similar size and scope) to develop and commercialize one or more products in the license field and to obtain any necessary governmental approvals in respect of, and market the products in license field, if any. Additionally, we have assumed certain development and regulatory milestone obligations. We must report on our progress towards achieving these milestones on an annual basis. We may unilaterally terminate the license agreement at any time by sending Institut Pasteur 90 days prior written notice. Either party may terminate the license in the event of the other party's substantial breach which remains uncured after 60 days of receiving written notice of such breach. Institut Pasteur may also terminate the agreement in the event bankruptcy proceedings are opened against us and not dismissed within 60 days.

Absent early termination, the agreement will automatically terminate upon the expiration of the last licensed patents or five years after first market authorization of the first product, whichever occurs later. In the event the agreement is terminated, while the license grant would cease, we would retain the right to manufacture, import, use and sell licensed products for a certain period of time post-termination. In addition, our ownership stake in certain jointly made improvements covered by the licensed patents would survive termination of the agreement. The longest lived patent rights licensed to us under the agreement are currently expected to expire in 2023.

***Stanford University***

In July 2002, we entered into a non-exclusive license agreement with the Board of Trustees of the Leland Stanford Junior University, referred to herein as Stanford, which we amended and restated in April 2012. Under this agreement, we are granted a license to use the HEK293T cell line for any commercial or non-commercial use for research, nonclinical and clinical development purpose and human and animal gene therapy products.

We have the right to grant sublicenses outright to third parties under the agreement. For each such sublicense we grant, we must pay Stanford a fee (unless the sublicense is to a collaborating partner, contract manufacturer or contract research organization).

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin, Lenti-D, bb2121 and bb21217 product candidates, we will be obligated to pay Stanford a percentage of net sales as a royalty. This royalty varies with net sales but in any event is in the low single digits and is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage which is less than one percent. Since April 2013, we have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.

We may unilaterally terminate the agreement by giving Stanford 30 days' written notice. Stanford may also terminate the license agreement if after 30 days of providing notice we are delinquent on any report or payment, are not using commercially reasonable efforts to develop, manufacture and/or commercialize one or more licensed products, are in material breach of any provision or provide any false report. Termination of this agreement may require us to utilize different cell types for vector manufacturing, which could lead to delays.

Absent early termination, the license will expire in April 2037. We may elect to extend the term for an additional 25 years so long as we have a commercial product on the market at that time and we are in material compliance with the license agreement.

***Massachusetts Institute of Technology***

In December 1996, we entered into an exclusive license with the Massachusetts Institute of Technology, referred to herein as MIT, for use of certain patents in any field. This license agreement was amended in December 2003, May 2004 and June 2011. The licensed patent portfolio includes at least 18 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date from 2017-2023. This license also has been amended to include a case jointly owned by MIT and us wherein we received the exclusive license to MIT's rights in this case. MIT retains the right to practice the intellectual property licensed under the agreement for noncommercial research purposes.

We have the right to grant sublicenses outright to third parties under the agreement. In the event we sublicense the patent rights, we must pay MIT a percentage of all payments we receive from by the sublicensee. This percentage varies from mid-single digits to low double digits.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin product candidate, we will be obligated to pay MIT a percentage of net sales by us or our sublicensees as a royalty. This royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one-percent. In addition, we make under this agreement an annual maintenance payment which may be credited against the royalty payments.

We are required to use diligent efforts to market licensed products and to continue active, diligent development and marketing efforts for licensed products during the term of the agreement. We have assumed certain milestones with respect to raising capital investment and regulatory progress. We must report on our progress on achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement upon six months' notice to MIT. MIT may terminate the agreement if we cease to carry on our business, or in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment). In the event the agreement is terminated, while the license grant would cease, we would retain a right to complete manufacture of any licensed products in process and sell then-existing inventory. In addition, MIT would grant our sublicensees a direct license following such termination. With respect to jointly owned intellectual property, any termination would allow MIT to grant licenses to any third party to such intellectual property, without our approval, unless a sublicensee was already in place, in which case, MIT would grant our sublicensees a direct license.

### ***Research Development Foundation***

In December 2011, we entered into an exclusive license with RDF to use certain patents that involve lentiviral vectors. The RDF licensed patent portfolio includes at least 29 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2021 and 2027. RDF retains the right, on behalf of itself and other nonprofit academic research institutions, to practice and use the licensed patents for any academic, non-clinical research and educational purposes. We have the right to grant sublicenses outright to third parties under the agreement.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include both our Lenti-D, LentiGlobin, bb2121 and bb21217 product candidates, we are obligated to pay RDF a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced by half if during the following ten years from the first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

We are required to use commercially reasonable and diligent efforts for a company of our size and resources to develop or commercialize one or more licensed products, including our first licensed product by 2016 and a second licensed product by 2018. These diligence efforts include minimum annual royalty payments to RDF, which are creditable against earned royalties otherwise due to RDF, and payments upon regulatory milestones.

RDF may terminate the agreement in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment) or in the event we become bankrupt, our business or assets or property are placed in the hands of a receiver, assignee or trustee, we institute or suffer to be instituted any procedure in bankruptcy court for reorganization or rearrangement of our financial affairs, make a general assignment for the benefit of creditors, or if we or an affiliate or a sublicensee institutes any procedure challenging the validity or patentability of any patent or patent application within the licensed patents, the agreement will immediately terminate.

Absent early termination, the agreement will continue until its expiration upon the later of there being no more valid claims within the licensed patents or the expiration of our royalty obligations on licensed products that are subject to an earned royalty, if such earned royalty is based on the minimum 10-year royalty period described above. In the event the agreement is terminated, while the license grant would cease, RDF will grant our sublicensees a direct license. The longest lived patent rights licensed to us under the agreement are in one U.S. patent currently expected to expire in 2027.

### ***Biogen***

In August 2014, we entered into a license agreement with Biogen, pursuant to which we co-exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2020 and 2032. Biogen retains the right to practice and use the licensed patents in the licensed field and territory. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our bb2121 and bb21217 product candidates, we will be obligated to pay Biogen a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$24.0 million in the aggregate for each licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to Biogen. Either party may terminate the license in the event of the other party's material breach upon notice and an opportunity for the breaching party to cure. Either party may also terminate the agreement in the event bankruptcy proceedings are opened against the other party and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of all patent rights covered by the agreement or ten years from the date of first commercial sale of a licensed product, whichever is later. The longest lived patent rights licensed to us under the Agreement are in a U.S. patent, currently expected to expire in 2032.

### ***NIH***

In August 2015, we entered into a license agreement with the NIH, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033. NIH retains the right to practice the intellectual property licensed under the agreement on behalf of the government of the United States. We have the right to grant sublicenses to third parties, subject to certain conditions. For each such sublicense we grant we must pay the NIH a fee. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our bb2121 and bb21217 product candidates, we will be obligated to pay the NIH a percentage of net sales as a royalty in the low single digits. We are required to use

commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$9.7 million in the aggregate for a licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to the NIH. The NIH may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. The NIH may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of the patent rights covered by the agreement. The longest lived patent rights licensed to us under the Agreement are currently expected to expire in 2033.

#### **SIRION**

In December 2015, we entered into a license agreement with SIRION, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of manufacturing gene therapy products. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include our LentiGlobin product candidate, we will be obligated to pay SIRION a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement, and we must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$13.4 million in the aggregate upon the achievement of certain development and regulatory milestones. We may unilaterally terminate the license agreement at any time with prior written notice to SIRION. SIRION may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. SIRION may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of the patent rights covered by the agreement. The longest lived patent rights licensed to us under the Agreement are currently expected to expire in 2033.

#### **Orchard Therapeutics Limited**

In April 2017, we entered into a license agreement with GlaxoSmithKline Intellectual Property Development Limited, or GSK, pursuant to which GSK non-exclusively licensed certain of our patent rights related to lentiviral vector technology to develop and commercialize gene therapies for Wiscott-Aldrich syndrome and metachromatic leukodystrophy, two rare genetic diseases. Effective April 2018, this license agreement was assigned by GSK to Orchard Therapeutics Limited, or Orchard. Financial terms of the agreement include an upfront payment to us as well as potential development and regulatory milestone payments and low single digit royalties on net sales of covered products.

#### **Novartis Pharma AG**

In April 2017, we entered into a license agreement with Novartis Pharma AG, or Novartis, pursuant to which Novartis non-exclusively licensed certain of our patent rights related to lentiviral vector technology to develop and commercialize chimeric antigen receptor T cell (CAR T) therapies for oncology, including Novartis' approved CAR T therapy Kymriah. Financial terms of the agreement include an upfront payment to us as well as potential development and regulatory milestone payments and low single digit royalties on net sales of covered products.

#### **Competition**

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. We face potential competition from many different sources, including larger and better-funded pharmaceutical and biotechnology companies. Not only must we compete with other companies that are focused on gene therapy products but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future.

There are other organizations working to improve existing therapies or to develop new therapies for our initially selected indications. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, and our preclinical T cell-based cancer immunotherapy product candidates. These efforts include the following:

- **β-thalassemia:** The current standard of care for the treatment of β-thalassemia in the developed world is chronic blood transfusions to address the patient's anemia. In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with their chronic blood transfusions. Novartis and ApoPharma Inc., who provide the leading iron chelation therapy, are seeking to develop improvements to their product profile and accessibility. A number of different approaches are under investigation that seek to improve the current standard of care treatment options, including, a protein that aims to improve red blood cell production and fetal hemoglobin regulators. Acceleron Pharma, Inc. (in collaboration with Celgene) is investigating luspatercept (ACE-536), a subcutaneously-delivered protein therapeutic that targets molecules in the TGF-β superfamily, which is currently in two phase 3 clinical trials in subjects with transfusion dependent β-thalassemia (TDT) and non-transfusion dependent β-thalassemia. Acceleron and Celgene are planning regulatory submissions of luspatercept in the United States and Europe in the first half of 2019. In addition, some patients with β-thalassemia receive HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. In addition, there are a number of academic and industry-sponsored research and development programs to improve the outcomes of allogeneic HSCT, or the tolerability and safety of haploidentical HSCT, while increasing the availability of suitable donors. These programs include a modified donor T cell therapy to be used in conjunction with haploidentical HSCT that is in an ongoing phase 1/2 study supported by Bellicum Pharmaceuticals, Inc.; and an adjunctive T cell immunotherapy treatment in conjunction with allogeneic HSCT that is in ongoing phase 2 and 3 studies supported by Kiadis Pharma. There are also several different groups developing other approaches for β-thalassemia, including one that uses a similar *ex vivo* autologous gene therapy approach, but uses a different vector and different cell processing techniques and two that use gene editing approaches. These include: the San Raffaele Telethon Institute for Gene Therapy (in collaboration with Orchard Therapeutics) is currently investigating its gene therapy in a phase 2 study of adults and pediatric patients with in transfusion dependent β-thalassemia (TDT); Sangamo BioSciences Inc. (in collaboration with Bioverativ Inc., a Sanofi company) is investigating ST-400, using a zinc finger nuclease-mediated gene-editing approach currently in an ongoing phase 1/2 study; and CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated) is conducting an ongoing phase 1/2 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer.
- **Sickle cell disease:** The current standard of care for the treatment of SCD in the developed world is chronic blood transfusions or hydroxyurea (a generic drug). In addition, patients treated with chronic blood transfusions often receive iron chelation therapy to help manage the iron overload. Emmaus Life Sciences, Inc. recently received FDA approval for and have launched Endari (L-glutamine). We are aware of ongoing studies that continue to evaluate the efficacy and safety of hydroxyurea in various populations. In addition, a limited number of patients with SCD receive allogeneic HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. In addition, there are a number of academic and industry-sponsored research and development programs to improve the tolerability and safety of allogeneic HSCT with less well-matched sources of donor cells, while increasing the availability of suitable donors. These programs include a modified donor T cell therapy to be used in conjunction with haploidentical HSCT that is in an ongoing phase 1/2 study supported by Bellicum Pharmaceuticals, Inc. A number of different therapeutic approaches are under investigation targeting the various aspects of SCD pathophysiology, including: antibodies to p-selectin including crizanlizumab currently in a phase 3 study supported by Novartis; hemoglobin modifiers to prevent the sickling of RBC, including voxelotor (GBT440) in an ongoing phase 3 study supported by Global Blood Therapeutics, Inc.; pan-selectin inhibitors, including rivipansel (GMI-1070) in phase 3 studies supported by GlycoMimetics Inc. (in 2011, Pfizer Inc. and GlycoMimetics Inc. entered a global collaboration to advance this compound); and also gene editing approaches being supported by Intellia Therapeutics, Inc. (in collaboration with Novartis), Editas Medicine, Inc. and CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated); and Sangamo BioSciences Inc. (in collaboration with Bioverativ). There are also several different groups developing gene therapy approaches for SCD. Some of these groups use a similar *ex vivo* autologous approach, but make use of different vectors and different cell processing techniques. These include: UCLA, which has received funding from the California Institute of Regenerative Medicine to pursue a phase 1 gene therapy study for SCD; and Aruvant Sciences, Inc.'s RVT-181, currently in a phase 1/2 gene therapy study for SCD.
- **CALD:** The current standard of care for the treatment of CALD is allogeneic HSCT. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT, such as Magenta Therapeutic, Inc.'s cord blood expansion technology which is currently being investigated in a phase 2 clinical trial for the treatment of inherited metabolic disorders, including adrenoleukodystrophy. Other possible treatments being investigated include Viking Therapeutics, Inc.'s VK0214, a selective thyroid receptor-β agonist, and Orpheris, Inc.'s OP-101.

- **Multiple Myeloma:** The current standard of care for relapsed and refractory multiple myeloma includes IMIDs (e.g., thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), monoclonal antibodies (e.g., daratumumab, elotuzumab), cytotoxic agents, and HSCT. There are several groups developing autologous T cell therapies for relapsed and refractory multiple myeloma that use a similar autologous *ex vivo* approach, but a different target antigen, BCMA single-chain variable fragment or, we believe, cell processing techniques. These programs include: an anti-BCMA CAR T cell therapy that is currently in a single-center phase 1 study by the University of Pennsylvania (in collaboration with Novartis AG); an anti-BCMA CAR T cell therapy that is in a phase 1b/2 study in the United States (Nanjing Legend in collaboration with Janssen Biotech); a BCMA and TACI-targeted CAR T cell therapy that is currently in a phase 1/2 study (Autolus); an anti-BCMA CAR T cell therapy that is in phase 1 study (Poseida Therapeutics, Inc.); and an anti-BCMA CAR T cell therapy in clinical development (phase 1/2) sponsored by Celgene following the completion of its acquisition of Juno Therapeutics, Inc. In addition to these autologous T cell-based approaches, Allogene Therapeutics, Inc., Poseida, and CRISPR Therapeutics have disclosed preclinical programs for allogeneic BCMA CAR T cell therapies. There are also therapies using other modalities being developed by several groups, including two bispecific T cell engagers currently in phase 1 studies supported by Amgen Inc., a bispecific antibody therapy currently in a phase 1 study supported by Janssen Research and Development, LLC, a specific antibody therapy currently in a phase 1 study supported by Pfizer, Inc., and an antibody drug conjugate therapy currently in a phase 2 study supported by GSK, and those being developed in preclinical programs.
- **T cell-based immunotherapies in oncology:** A number of pharmaceutical companies and academic collaborators are researching and developing T cell-based immunotherapies in oncology, in addition to the multiple myeloma programs described above. These include: Novartis AG (in collaboration with the University of Pennsylvania), Adaptimmune Inc., Celgene following its acquisition of Juno Therapeutics, Inc., Gilead Sciences, Inc. (in collaboration with the National Institutes of Health), Pfizer Inc. (through their collaboration with Cellectis SA and Servier), Amgen, Inc., among others. Many of the T cell-based immunotherapy programs being developed by these companies are already in phase 1/2 clinical trials for multiple indications.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products.

#### **Government regulation**

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. FDA approval must be obtained before clinical testing of biological products, and each clinical study protocol for a gene therapy product is reviewed by the FDA. FDA approval also must be obtained before marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research, or the CBER, regulates gene therapy products. The CBER works closely with the NIH. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

#### ***U.S. biological products development process***

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, in the past, a protocol and related documentation was submitted to and the study was registered with the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Pursuant to the current NIH Guidelines, research involving recombinant or synthetic nucleic acid molecules must be approved by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. Such trials remain subject to FDA and other clinical trial regulations, and only after FDA, IBC, and other relevant approvals are in place can these protocols proceed.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an IRB at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed.

Human clinical studies are typically conducted in three sequential phases that may overlap or be combined:

- *phase 1.* The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *phase 2.* The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *phase 3.* Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Post-approval clinical studies, sometimes referred to as phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, phase 2 and phase 3 clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical studies, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

#### ***U.S. review and approval processes***

After the completion of clinical studies of a biological product, FDA approval of a BLA, must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, as amended, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, withdraw the application, or request a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as phase 4 clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of standard BLAs in 10 months and 90% of priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

#### ***Orphan drug designation***

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

#### ***Expedited development and review programs***

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

#### ***Regenerative medicine advanced therapies (RMAT) designation***

As part of the 21st Century Cures Act, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine advanced therapies do not include those human cells, tissues, and cellular and tissue based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval.

#### ***Post-approval requirements***

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to GMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the GMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of GMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval. In addition, companies that manufacture or distribute drug or biological products or that hold approved BLAs must comply with other regulatory requirements, including submitting annual reports, reporting information about adverse drug experiences, and maintaining certain records. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, including a REMS or the conduct of post-marketing studies to assess a newly-discovered safety issue.

We also must comply with the FDA's and other jurisdiction's advertising and promotion requirements, such as those related to direct-to-consumer advertising and advertising to healthcare professionals, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. Consequences could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with healthcare professionals, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

#### ***U.S. patent term restoration and marketing exclusivity***

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

#### **Fraud and Abuse Laws**

In addition to restrictions on marketing of pharmaceutical products, several other types of state/ federal laws and trade association membership codes of conduct have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include anti-kickback and false claims statutes. The U.S. federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any healthcare item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging healthcare professionals or patients as speakers or consultants, may be subject to scrutiny if they do not fit squarely within the exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient assistance programs.

The U.S. federal civil False Claims Act prohibits, among other things, any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using, or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. In recent years, several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for, among other things, allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have faced enforcement actions for causing false claims to be submitted because of the company's marketing the product for unapproved, and thus non-reimbursable, uses. Federal enforcement agencies also have showed increased interest in pharmaceutical companies' product and patient assistance programs, including reimbursement and co-pay support services, and a number of investigations into these programs have resulted in significant civil and criminal settlements. In addition, the Affordable Care Act amended federal law to provide that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Criminal prosecution is possible for making or presenting a false or fictitious or fraudulent claim to the federal government.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created several new federal crimes, including healthcare fraud and false statements relating to healthcare matters. The healthcare fraud statute prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

The majority of states also have statutes or regulations similar to the federal anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. Several states now require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes.

The U.S. federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to engage in extensive tracking of payments and other transfers of value to prescribers and teaching hospitals, including physician ownership and investment interests, and public reporting of such data. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program are required to track such payments, and must submit a report on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year. A number of other countries, states and municipalities have also implemented additional payment tracking and reporting requirements, which if not done correctly may result in additional penalties.

In addition, the U.S. Foreign Corrupt Practices Act, or the FCPA, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any official of another country, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in that capacity. In many other countries, healthcare professionals who prescribe pharmaceuticals are employed by government entities, and the purchasers of pharmaceuticals are government entities. Our dealings with these prescribers and purchasers may be subject to the FCPA.

Other countries, including a number of EU member states, have laws of similar application, including anti-bribery or anti-corruption laws such as the UK Bribery Act. The UK Bribery Act prohibits giving, offering, or promising bribes to any person, as well as requesting, agreeing to receive, or accepting bribes from any person. Under the UK Bribery Act, a company that carries on a business or part of a business in the United Kingdom may be held liable for bribes given, offered or promised to any person in any country by employees or other persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability under the UK Bribery Act is strict, but a defense of having in place adequate procedures designed to prevent bribery is available.

Because of the breadth of these various fraud and abuse laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have material adverse effects on our business, financial condition and results of operations. In the event governmental authorities conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations, they may impose sanctions under these laws, which are potentially significant and may include civil monetary penalties, damages, exclusion of an entity or individual from participation in government health care programs, criminal fines and imprisonment, as well as the potential curtailment or restructuring of our operations. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

#### ***Government regulation outside of the United States***

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical study may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The EMA has established the Adaptive Pathways pilot program intended to expedite or facilitate either an initial approval of a medicinal product in a well-defined patient subgroup with a high medical need and subsequent iterative expansion of the indication to a larger patient population, or an early regulatory approval (e.g., conditional approval), which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on a medicinal product's use in patients. The approach builds on regulatory processes already in place within the existing EU legal framework.

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an “orphan medicinal product” in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

In the EU, the advertising and promotion of our products will also be subject to EU member states’ laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, as well as other EU member state legislation that may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product’s approved labeling. The off-label promotion of medicinal products is prohibited in the EU. The applicable laws at the EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict communications concerning the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with healthcare professionals.

Failure to comply with the EU member state laws implementing the Community Code on medicinal products, and EU rules governing the promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, with the EU member state laws that apply to the promotion of medicinal products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements can result in enforcement action by the EU member state authorities, which may include any of the following: fines, imprisonment, orders forfeiting products or prohibiting or suspending their supply to the market, or requiring the manufacturer to issue public warnings, or to conduct a product recall.

The national laws of certain EU member states require payments made to physicians to be publicly disclosed. Moreover, the European Federation of Pharmaceutical Industries and Associations, or EFPIA, Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organizations imposes a general obligation on members of the EFPIA or related national industry bodies to disclose transfers of value to healthcare professionals. In addition, agreements with physicians must often be the subject of prior notification and approval by the physician’s employer, his/her competent professional organization, and/or the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU member states.

For other countries outside of the EU, such as countries in Eastern Europe, Central and South America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. This act could have implications for our interactions with physicians in and outside the UK. In all cases, again, the clinical trials are conducted in accordance with GCP, applicable regulatory requirements, and ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, warning letters or untitled letters, injunctions, civil, administrative, or criminal penalties, monetary fines or imprisonment, suspension or withdrawal of regulatory approvals, suspension of ongoing clinical studies, refusal to approve pending applications or supplements to applications filed by us, suspension or the imposition of restrictions on operations, product recalls, the refusal to permit the import or export of our products or the seizure or detention of products.

### Pricing, Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors and/or governments. Third-party payors can include government healthcare systems, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payors may provide coverage, but place stringent limitations on such coverage, such as requiring alternative treatments to be tried first. These third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety, efficacy, and overall value. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. Our product candidates may not be considered medically reasonable or necessary or cost-effective. Even if a drug product is covered, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the United States and foreign governments continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of drug products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate systems under which products may be marketed only after a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of studies or analyses of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to set their own prices for medicines, but exert cost controls in other ways, including but not limited to, placing revenue caps on product sales, providing reimbursement for only a subset of eligible patients, mandating price negotiations after a set period of time, or mandating that prices not exceed an average basket of prices in other countries. The downward pressure on health care costs in general, particularly treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, European governments may periodically review and decrease prices based on factors, including but not limited to, years-on-market, price in other countries, competitive entry, new clinical data, lack of supporting clinical data, or other factors.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

We have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as our LentiGlobin product candidate. While we are engaged in discussions with potential payors, there is no assurance that any payors will adopt these payment models. Even with these payment models, there may be substantial resistance to the cost of our products by payors and the public generally. These payment models may not be sufficient for payors to grant coverage, and if we are unable to obtain adequate coverage for our products, the adoption of our products and access for patients may be limited. In addition, to the extent reimbursement for our products is subject to outcomes-based arrangements, our future revenues from product sales will be more at risk. These factors could affect our ability to successfully commercialize our products and adversely impact our business, financial condition, results of operations and prospects.

## **Employees**

As of January 31, 2019, we had 764 full-time employees, 153 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 540 employees are engaged in research and development activities and 224 employees are engaged in commercial, finance, legal, business development, human resources, information technology, facilities and other general administrative functions. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

## **Corporate Information**

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. Our mailing address and executive offices are located at 60 Binney Street, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: [www.bluebirdbio.com](http://www.bluebirdbio.com). The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

### **Item 1A. Risk Factors**

*An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.*

### **Risks related to the development of our product candidates**

***Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.***

We have concentrated our therapeutic product research and development efforts on our gene therapy platform, and our future success depends on the successful development of this therapeutic approach. There can be no assurance that any development problems we experience in the future related to our gene therapy platform will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible and commercial-scale manufacturing process or transferring that process to commercial partners, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical study requirements of the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied pharmaceutical or other product candidates. Currently, a limited number of gene therapy products, including CAR T therapies, have been approved by the FDA, the EMA and the European Commission. Given the few precedents of approved gene therapy products, it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, the EU or other jurisdictions. Approvals by the EMA and the European Commission may not be indicative of what the FDA may require for approval.

Regulatory requirements governing the development of gene therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Tissues and Advanced Therapies within the CBER, to consolidate the review of gene therapy and related products, and to advise the CBER on its review. The FDA can put an investigational new drug application, or IND, on clinical hold if the information in an IND is not sufficient to assess the risks in pediatric patients. Before a clinical study can begin at any institution, that institution's IRB, and its Institutional Biosafety Committee will have to review the proposed clinical study to assess the safety of the study. Moreover, serious adverse events or developments in clinical trials of gene therapy product candidates conducted by others may cause the FDA or other regulatory bodies to initiate a clinical hold on our clinical trials or otherwise change the requirements for approval of any of our product candidates.

These regulatory review agencies, committees and advisory groups and the new requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional or larger studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval studies, limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

***Success in early clinical studies may not be indicative of results obtained in later studies.***

Results from previous or ongoing studies are not necessarily predictive of our future clinical study results, and initial or interim results may not continue or be confirmed upon completion of the study. There is limited data concerning long-term safety and efficacy following treatment with our gene therapy and T cell-based product candidates. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical studies, and may not be repeated or observed in ongoing or future studies involving our product candidates. For instance, while patients with TDT who have been treated with our LentiGlobin product candidate may experience a reduction or temporary elimination of transfusion support, there can be no assurance that they will not require transfusion support in the future. Similarly, patients with relapsed and refractory multiple myeloma who have been treated with the bb2121 or the bb21217 product candidate may experience disease progression. We have experienced unexpected results in the past, and we may experience unexpected results in the future. For instance, initial results from our clinical studies of LentiGlobin suggested that patients with TDT and non- $\beta^0/\beta^0$  genotypes experienced better outcomes to treatment than patients with TDT and  $\beta^0/\beta^0$  genotypes. Consequently, we are seeking conditional approval in the EU, and we expect to seek FDA approval in the United States, of our LentiGlobin product candidate initially for the treatment of patients with TDT and non- $\beta^0/\beta^0$  genotypes. In order to support an application for FDA approval of our LentiGlobin product candidate in patients with TDT and  $\beta^0/\beta^0$  genotypes, we initiated the HGB-212 study, but we do not know if or when our LentiGlobin product candidate may be commercially available to patients with all genotypes. Furthermore, our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies. There can be no assurance that any of these studies will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates.

There is a high failure rate for drugs and biologics proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical studies even after achieving promising results in earlier stage clinical studies. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development.

***Even if we complete the necessary preclinical and clinical studies, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate or the approval may be for a more narrow indication than we expect.***

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical studies, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory advisory group or authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical studies and the review process. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

In October 2018, we announced that the EMA accepted the submission of our MAA of our LentiGlobin product candidate for the treatment of adult and adolescent patients with TDT and non- $\beta^0/\beta^0$  genotypes. Whether our LentiGlobin product candidate is eligible for conditional approval will ultimately be determined at the discretion of the EMA and European Commission, and will be dependent upon the data available, which may not be sufficiently robust from a safety and/or efficacy perspective to support conditional approval. The EMA may require that we conduct additional or larger clinical trials before our LentiGlobin product candidate is eligible for approval. Even if conditional approval is obtained, the conditions to be imposed on us under this program are unknown and will be imposed at the time of any such conditional approval.

In general, the FDA requires the successful completion of two pivotal trials to support approval of a BLA, but in certain circumstances, will approve a BLA based on only one pivotal trial. If successful, we believe the results from our ongoing Northstar-2 study, together with data from our Northstar study and ongoing HGB-205 study, could be sufficient to form the basis for a BLA submission for our LentiGlobin product candidate to treat adult and adolescent patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. In addition, if successful, we believe the results from our Northstar-3 study, together with data from our Northstar study and ongoing Northstar-2 study, could be sufficient to form the basis for a BLA supplement submission for our LentiGlobin product candidate to treat patients with TDT and  $\beta$ 0/ $\beta$ 0 genotypes. However, it should be noted that our ability to submit and obtain approval of a BLA is ultimately an FDA review decision, which will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support the submission or approval of a BLA. Depending on the outcome of these ongoing clinical studies, the FDA may require that we conduct additional or larger pivotal trials before we can submit or obtain approval for a BLA for our LentiGlobin product candidate for the treatment of TDT.

Based on our discussions with the FDA and EMA, we believe that we may be able to seek approval for our Lenti-D product candidate for the treatment of patients with CALD on the basis of the clinical data from our ongoing Starbeam study, and the ongoing ALD-103 observational study. Our regulatory submission plans are contingent upon our Lenti-D product candidate demonstrating sufficient efficacy and safety in the Starbeam study. Whether our Lenti-D product candidate is eligible for approval will ultimately be determined at the discretion of the FDA and EMA, and will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support approval. Depending on the outcome of our ongoing studies, the FDA in the United States and EMA and European Commission in the EU may require that we conduct additional or larger clinical trials before our Lenti-D product candidate is eligible for approval.

In the development of our LentiGlobin product candidate for the treatment of patients with SCD, we are exploring efficacy endpoints based on  $\beta$ A-T87Q expression and total hemoglobin, and the relationship such endpoints have with clinical outcomes. Our development plans in the United States are contingent upon our LentiGlobin product candidate demonstrating sufficient efficacy and safety in the ongoing HGB-206 study and planned HGB-210 study. Whether our LentiGlobin product candidate is eligible for approval will ultimately be determined at the discretion of the FDA and will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support approval. For instance, the FDA may not accept  $\beta$ A-T87Q expression and total hemoglobin as surrogate endpoints for other SCD clinical outcomes such as frequency of vaso-occlusive events. Depending on the outcome of our ongoing and planned studies, the FDA may require that we conduct additional or larger clinical trials before our LentiGlobin product candidate is eligible for approval for the treatment of patients with SCD. In addition, we are engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin in SCD in Europe, and we cannot be certain that our HGB-206 study and planned HGB-210 study will be sufficient to form the basis for an initial MAA submission in Europe for the treatment of patients with SCD.

***We may encounter substantial delays in our clinical studies or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.***

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity and potency, or efficacy, of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in obtaining required IRB or Institutional Ethics Committee approval at each clinical study site;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites or due to unforeseen safety issues;
- failure by our CROs, other third parties or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory requirements in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- failure to obtain sufficient cells from patients to manufacture enough drug product or achieve target cell doses;
- delays in having patients complete participation in a study or return for post-treatment follow-up;

- clinical study sites or patients dropping out of a study;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Furthermore, identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends on the speed at which we can recruit eligible patients to participate in testing our product candidates. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical studies in a timely manner. The conditions for which we plan to evaluate our current product candidates in severe genetic diseases are rare disorders with limited patient pools from which to draw for clinical studies. The eligibility criteria of our clinical studies will further limit the pool of available study participants, and the process of finding and diagnosing patients may prove costly. Patients may be unwilling to participate in our studies because of negative publicity from adverse events in the biotechnology or gene therapy industries or for other reasons, including competitive clinical studies for similar patient populations. We have experienced delays in some of our clinical studies in the past, and we may experience similar delays in the future.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to demonstrate comparability of our modified product candidates to earlier versions.

Clinical study delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If the results of our clinical studies are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining regulatory approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be required to perform additional clinical studies or clinical studies of longer duration to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its use;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Treatment with our gene therapy product candidates involves chemotherapy and myeloablative treatments, which can cause side effects or adverse events that are unrelated to our product candidates, but may still impact the perception of the potential benefits of our product candidates and the success of our clinical studies. Additionally, our product candidates could potentially cause other adverse events that have not yet been predicted. The inclusion of critically ill patients in our clinical studies may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using, or the progression of their disease. As described above, any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

***In previous clinical studies involving viral vectors for gene therapy, some subjects experienced serious adverse events, including the development of leukemia due to vector-related insertional oncogenesis. If our vectors demonstrate a similar effect, we may be required to halt or delay further clinical development of our product candidates.***

A significant risk in any gene therapy product based on viral vectors is that the vector will insert in or near cancer-causing oncogenes leading to uncontrolled clonal proliferation of mature cancer cells in the patient. In published studies, lentiviral vectors have demonstrated an improved safety profile over gamma-retroviral vectors used in early gene therapy studies, with no disclosed events of gene therapy-related adverse events, which we believe is due to a number of factors including the tendency of these vectors to integrate within genes rather than in areas that control gene expression, as well as their lack of strong viral enhancers. However, it should be noted that in a phase 1/2 study of HPV569, which utilized an earlier generation lentiviral vector of our LentiGlobin vector, we initially observed in one subject that a disproportionate number of the cells expressing our functional gene had the same insertion site. Tests showed that this partial clonal dominance contained an insertion of the functional gene in the HMGA2 gene that persisted for a period of two to three years. Although there was some initial concern that the observed clonal dominance might represent a pre-leukemic event, there have been no adverse clinical consequences of this event, or any signs of cancer, in over seven years since the observation was made. The presence of the HMGA2 clone has steadily declined in this subject over time to the point that it is no longer the most common clone observed in this subject.

Notwithstanding the historical data regarding the potential safety improvements of lentiviral vectors, the risk of insertional oncogenesis remains a significant concern for gene therapy and we cannot assure that it will not occur in any of our ongoing or planned clinical studies. There is also the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. The FDA has stated that lentiviral vectors possess characteristics that may pose high risks of delayed adverse events. If any such adverse events occur, further advancement of our clinical studies could be halted or delayed, which would have a material adverse effect on our business and operations.

***Patients receiving T cell-based immunotherapies such as our oncology product candidates bb2121 and bb21217, may experience serious adverse events, including neurotoxicity and cytokine release syndrome. If our product candidates are revealed to have high and unacceptable severity and/or prevalence of side effects or unexpected characteristics, their clinical development, regulatory approval, and commercial potential will be negatively impacted, which will significantly harm our business, financial condition and prospects.***

The bb2121 and bb21217 product candidates are chimeric antigen receptor, or CAR, T cell-based immunotherapies. In previous and ongoing clinical studies involving CAR T cell products, including those involving the bb2121 and bb21217 product candidates, patients experienced side effects such as neurotoxicity and cytokine release syndrome. There have been life threatening events related to severe neurotoxicity and cytokine release syndrome, requiring intense medical intervention such as intubation or pressor support, and in several cases, resulted in death. Severe neurotoxicity is a condition that is currently defined clinically by cerebral edema, confusion, drowsiness, speech impairment, tremors, seizures, or other central nervous system side effects, when such side effects are serious enough to lead to intensive care. In some cases, severe neurotoxicity was thought to be associated with the use of certain lymphodepletion regimens used prior to the administration of the CAR T cell products. Cytokine release syndrome is a condition that is currently defined clinically by certain symptoms related to the release of cytokines, which can include fever, chills, low blood pressure, when such side effects are serious enough to lead to intensive care with mechanical ventilation or significant vasopressor support. The exact cause or causes of cytokine release syndrome and severe neurotoxicity in connection with treatment of CAR T cell products is not fully understood at this time. In addition, patients have experienced other adverse events in these studies, such as a reduction in the number of blood cells (in the form of neutropenia, thrombocytopenia, anemia or other cytopenias), febrile neutropenia, chemical laboratory abnormalities (including elevated liver enzymes), and renal failure.

Undesirable side effects caused by the bb2121 or bb21217 product candidate, other CAR T product candidates targeting BCMA, or our other T cell-based immunotherapy product candidates, could cause us or regulatory authorities to interrupt, delay or halt clinical studies and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. In some cases, side effects such as neurotoxicity or cytokine release syndrome has resulted in clinical holds of ongoing clinical trials and/or discontinuation of the development of the product candidate. Results of our studies could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the studies or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from T cell-based immunotherapies are not normally encountered in the general patient population and by medical personnel. Medical personnel may need additional training regarding T cell-based immunotherapy product candidates to understand their side effects. Inadequate training in recognizing or failure to effectively manage the potential side effects of T cell-based immunotherapy product candidates could result in patient deaths. Any of these occurrences may harm our business, financial condition and prospects significantly.

***Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory scrutiny.***

Even if we obtain regulatory approval in a jurisdiction, the regulatory authority may still impose significant restrictions on the indicated uses or marketing of our product candidates, or impose ongoing requirements for potentially costly post-approval studies, post-market surveillance or patient or drug restrictions. For example, the FDA typically advises that patients treated with gene therapy undergo follow-up observations for potential adverse events for a 15-year period. Additionally, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices, or GMP, and adherence to commitments made in the BLA. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical studies;
- refuse to approve a pending marketing application, such as a BLA or supplements to a BLA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenues.

***The United Kingdom's decision to withdraw from the European Union could result in increased regulatory and legal complexity, which may make it more difficult for us to do business in Europe and impose additional challenges in securing regulatory approval of our product candidates in Europe.***

Negotiations for the United Kingdom's exit from the EU, or Brexit, has caused political and economic uncertainty, including in the regulatory framework applicable to our operations and potential products, and this uncertainty may persist for years. Brexit could, among other outcomes, disrupt the free movement of goods, services and people between the United Kingdom and the EU, and result in increased legal and regulatory complexities, as well as potential higher costs of conducting business in Europe. For instance, preparations for Brexit has resulted in the decision to move the EMA from the United Kingdom to the Netherlands, with operations currently scheduled to begin in the Netherlands by March 2019. This transition may cause disruption or delays in granting clinical trial authorization or opinions for marketing authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations.

The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and/or the United Kingdom. It is possible that there will be increased regulatory complexities which can disrupt the timing of our clinical trials and regulatory approvals. In addition, changes in, and legal uncertainty with regard to, national and international laws and regulations may present difficulties for our clinical and regulatory strategy. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenues and achieve and sustain profitability. In particular, we cannot predict whether, or the extent to which, Brexit will affect the timing for the potential commercial launch of our LentiGlobin product candidate in Europe in 2019.

In addition, as a result of Brexit, other European countries may seek to conduct referenda with respect to their continuing membership with the European Union. Given these possibilities and others we may not anticipate, as well as the absence of comparable precedent, it is unclear what financial, regulatory and legal implications the withdrawal of the United Kingdom from the European Union would have and how such withdrawal would affect us, and the full extent to which our business could be adversely affected.

#### Risks related to our reliance on third parties

*We expect to rely on third parties to conduct some or all aspects of our lentiviral vector production, drug product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.*

We do not expect to independently conduct all aspects of our lentiviral vector production, drug product manufacturing, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items. In some cases these third parties are academic, research or similar institutions that may not apply the same quality control protocols utilized in certain commercial settings.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical studies are conducted in accordance with the study plan and protocols, and that our lentiviral vectors and drug products are manufactured in accordance with GMP as applied in the relevant jurisdictions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines, conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, or manufacture our lentiviral vectors and drug products in accordance with GMP, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies and manufacturing process validation activities required to support future IND, MAA and BLA submissions and approval of our product candidates. Many of our agreements with these third parties contain termination provisions that allow these third parties to terminate their relationships with us at any time. If we need to enter into alternative arrangements, our product development and commercialization activities could be delayed.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- the risk that these activities are not conducted in accordance with our study plans and protocols;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

We may be forced to manufacture lentiviral vector and drug product candidates ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our lentiviral vector or drug product candidates may be unique or proprietary to the original manufacturer, and we may have difficulty or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

***We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.***

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Some components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA or MAA on a timely basis and where required, must adhere to the FDA's or other regulator's good laboratory practices, or GLP, and GMP regulations enforced by the FDA or other regulator through facilities inspection programs. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA or other regulatory approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other regulatory approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other regulators can impose regulatory sanctions including, among other things, refusal to approve a pending application for a biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. The number of manufacturers with the necessary manufacturing capabilities is limited. In addition, an alternative manufacturer would need to be qualified through a BLA supplement or similar regulatory submission which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenues.

***We are dependent on Celgene for the successful development and commercialization of bb2121 and bb21217. If Celgene does not devote sufficient resources to the development of bb2121 and bb21217, is unsuccessful in its efforts, or chooses to terminate its agreements with us, our business will be materially harmed.***

We are co-developing and co-promoting the bb2121 product candidate in the United States with Celgene under our amended and restated co-development and co-promotion agreement with Celgene, or the bb2121 CCPS. Under the bb2121 CCPS, we and Celgene share the obligation to develop and commercialize the bb2121 product candidate in the United States, and we will be solely dependent on Celgene to develop and commercialize bb2121 outside of the United States.

In addition, we have exclusively licensed to Celgene the right to develop and commercialize the bb21217 product candidate, and we retain an option to co-develop and co-promote bb21217 in the United States under our license agreement with Celgene. With respect to bb21217, we are responsible for completing the ongoing CRB-402 study, but Celgene is responsible for further clinical development and commercialization costs, unless we choose to exercise our option to co-develop and co-promote bb21217 in the United States. If we exercise our option to co-develop and co-promote bb21217 in the United States, we and Celgene will share the obligation to develop and commercialize bb21217 in the United States, and we will be solely dependent on Celgene to develop and commercialize bb21217 outside of the United States.

In our partnership with Celgene, Celgene is obligated to use commercially reasonable efforts to develop and commercialize bb2121 and bb21217. Celgene may determine however, that it is commercially reasonable to de-prioritize or discontinue the development of bb2121 and bb21217. These outcomes may occur for many reasons, including internal business reasons (including due to the existence of other Celgene programs that are potentially competitive with bb2121 and bb21217), results from clinical trials or because of unfavorable regulatory feedback. Further, on review of the safety and efficacy data, the FDA may impose requirements on the clinical trial program that render such a program commercially nonviable. In addition, under our agreements with Celgene, Celgene has certain decision-making rights in determining the development and commercialization plans and activities for that product candidate. We may disagree with Celgene about the development strategy it employs, but we will have limited rights to impose our development strategy on Celgene. Similarly, Celgene may decide to seek regulatory approval for, and limit commercialization of, bb2121 or bb21217 to narrower indications than we would pursue. More broadly, if Celgene elects to discontinue the development of bb2121 or bb21217, we may be unable to advance the product candidate ourselves. We would also be prevented from developing or commercializing another CAR T cell-based product candidate that targets BCMA outside of our collaboration with Celgene.

This partnership may not be scientifically or commercially successful for us due to a number of important factors, including the following:

- Celgene has wide discretion in determining the efforts and resources that it will apply to its partnership with us. The timing and amount of any development milestones, and downstream commercial profits, milestones and royalties that we may receive under such partnership will depend on, among other things, Celgene's efforts, allocation of resources and successful development and commercialization of bb2121, bb21217 and other product candidates that are the subject of its collaboration with us.
- Celgene may develop and commercialize, either alone or with others, products that are similar to or competitive with bb2121, bb21217 and other product candidates that are the subject of its collaboration with us. For example, Celgene is currently commercializing certain of its existing products, including lenalidomide and pomalidomide, for certain patients with relapsed and refractory multiple myeloma and is also developing JCAR-H125, another CAR-T product candidate targeting BCMA that it obtained through its acquisition of Juno Therapeutics, Inc. in March 2018.
- Celgene may terminate its partnership with us without cause and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities.
- Celgene may develop or commercialize our product candidates in such a way as to elicit litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability.
- Celgene may not comply with all applicable regulatory requirements, or may fail to report safety data in accordance with all applicable regulatory requirements.
- If Celgene were to breach its arrangements with us, we may need to enforce our right to terminate the agreement in legal proceedings, which could be costly and cause delay in our ability to receive rights back to the relevant product candidates. If we were to terminate an agreement with Celgene due to Celgene's breach or Celgene terminated the agreement without cause, the development and commercialization of bb2121 or bb21217 product candidates that are the subject of its collaboration with us could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue development and commercialization of these product candidates on our own if we choose not to, or are unable to, enter into a new collaboration for these product candidates.

Celgene may enter into one or more transactions with third parties, including a merger, consolidation, reorganization, sale of substantial assets, sale of substantial stock or other change in control, which could divert the attention of its management and adversely affect Celgene's ability to retain and motivate key personnel who are important to the continued development of the programs under the strategic partnership with us. In addition, the third-party to any such transaction could determine to reprioritize Celgene's development programs such that Celgene ceases to diligently pursue the development of our programs and/or cause the respective collaboration with us to terminate. In January 2019, Celgene announced that it has entered into a definitive merger agreement under which Bristol-Myers Squibb Company, or BMS, will acquire Celgene, and that the transaction is expected to be completed in the third quarter of 2019. The acquisition of Celgene by BMS may result in organizational and personnel changes, shifts in business focus or other developments that may have a material adverse effect on our collaboration with Celgene. There is no guarantee that BMS will place the same emphasis on the collaboration or on the development and commercialization of the bb2121 or bb21217 product candidates.

*We expect to rely on third parties to conduct, supervise and monitor our clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.*

We expect to rely on CROs and clinical study sites to ensure our clinical studies are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical studies may be deemed unreliable and the FDA may require us to perform additional clinical studies before approving any marketing applications.

If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical studies may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

*Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.*

Because we rely on third parties to manufacture our vectors and our product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

#### Risks related to our financial condition and capital requirements

*We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.*

We are a clinical-stage biotechnology company, and we have incurred net losses in each year since our inception in 1992, including net losses of \$555.6 million for the year ended December 31, 2018. As of December 31, 2018, we had an accumulated deficit of \$1.5 billion. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to generate revenues. We have devoted significant financial resources to research and development, including our clinical and preclinical development activities, which we expect to continue for the foreseeable future. To date, we have financed our operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. We do not expect to generate any product revenues until the second half of 2019, assuming we receive marketing approval for LentiGlobin in the EU. Even if we obtain regulatory approval to market a product candidate, our future revenues will depend upon the size of any markets in which our product candidates have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payors and adequate market share for our product candidates in those markets. In addition, to the extent payment for our products is subject to outcomes-based arrangements, our future cash collection and revenues from product sales will be at risk.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and preclinical and clinical development of our product candidates, including the bb2121 product candidate that we are co-developing with Celgene;
- establish capabilities to support our planned commercialization efforts, including establishing a sales, marketing and distribution infrastructure in the United States and Europe, and commercialize any products for which we may obtain marketing approval;
- obtain, build and expand manufacturing capacity, including capacity at third-party manufacturers and our own manufacturing facility;
- initiate additional research, preclinical, clinical or other programs as we seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel; and
- experience any delays or encounter issues with any of the above.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

***We have never generated any revenue from product sales and may never be profitable.***

Our ability to generate revenues and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory, pricing and reimbursement approvals necessary to commercialize our product candidates. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable, commercial-scale, reproducible, and transferable manufacturing process for our vectors and product candidates;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and commercial demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing a field-based team, marketing and distribution infrastructure;
- obtaining sufficient pricing and reimbursement for our product candidates from private and governmental payors;
- obtaining market acceptance and adoption of our product candidates and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;
- identifying and validating new product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; and
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how.

We expect to continue to incur significant expenditures for the foreseeable future, and we expect these expenditures to increase as we prepare for any potential commercial launch. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate, which costs may increase with any increased competition. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

***From time to time, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.***

We are currently advancing the LentiGlobin, Lenti-D, bb2121 and bb21217 product candidates through clinical development and other product candidates through preclinical development. Developing gene therapy products is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates in clinical studies.

As of December 31, 2018, our cash, cash equivalents and marketable securities were \$1.9 billion. We expect that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our current planned operations into 2022. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic objectives.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

#### **Risks related to commercialization of our product candidates**

***We rely on a complex supply chain for our product candidates. The manufacture and delivery of our engineered autologous gene therapy product presents significant challenges for us, and we may not be able to produce our vector and products at the quality, quantities, locations or timing needed to support commercialization.***

In order to develop our product candidates, apply for regulatory approvals and commercialize our products if approved, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We currently rely on third parties to manufacture the vector and the drug product candidate that we require for any clinical trials that we initiate. Although we intend to rely on a mix of internal and third-party manufacturers to support our planned commercialization efforts, we are still in the process of building out our internal capacity and have not secured commercial-scale manufacturing capacity in all of the regions where we intend to commercialize our potential products. By building our own internal manufacturing facility, we have incurred substantial expenditures and expect to incur significant additional expenditures in the future. In addition, there are many risks inherent in the construction of a new facility that could result in delays and additional costs, including the need to obtain access to necessary equipment and third-party technology, if any. Also, we have had to, and will continue to, hire and train qualified employees to staff our manufacturing facility. We may not be able to timely or successfully build out our internal capacity or negotiate binding agreements at commercially reasonable terms with third-party manufacturers.

The manufacture of our lentiviral vector and drug product candidates is complex and requires significant expertise. Manufacturers of cell therapy products often encounter difficulties in production, particularly in scaling out and validating initial production, and ensuring that the product meets required specifications. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot make any assurances that these problems will not occur in the future, or that we will be able to resolve or address problems that occur in a timely manner or with available funds. Furthermore, our cost of goods development is at an early stage. The actual cost to manufacture our lentiviral vector and drug product candidates could be greater than we expect and could materially and adversely affect the commercial viability of our product.

candidates. If we or such third-party manufacturers are unable to produce the necessary quantities of lentiviral vector and our product candidates, or in compliance with GMP or other pertinent regulatory requirements, and within our planned time frame and cost parameters, the development and sales of our products, if approved, may be materially harmed. Furthermore, if we or our third-party manufacturers are unable to produce the necessary quantities of viral vectors or our product candidates in quantities, quality requirements, or within the time frames that we need to support our commercialization activities, it may result in delays in our development plans or increased capital expenditures.

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have agreements with suppliers. There are a small number of suppliers for certain key materials that are used to manufacture our product candidates. Such suppliers may not sell these key materials to us or to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these key materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these key materials.

Additionally, since the HSCs and T cells have a limited window of stability following procurement from the subject, we must establish transduction facilities in the regions where we wish to commercialize our product. Currently, we rely on third-party contract manufacturers in the United States and Europe to produce our product candidates for our clinical studies. Since a portion of our target patient populations will be outside the United States and Europe, we will need to establish additional transduction facilities that can replicate our transduction process in order to address those patient populations. Establishment of such facilities may be financially impractical or impeded by technical, quality, or regulatory issues related to these new sites and we may also run into technical or scientific issues related to transfer of our transduction process or other developmental issues that we may be unable to resolve in a timely manner or with available funds.

Our commercial plan is to engage apheresis centers in our key launch regions as qualified treatment centers for the collection of patient HSCs and infusion of the drug product once manufactured. To ensure that the qualified treatment centers are prepared to collect patient HSCs and to ship them to our transduction facilities in accordance with our specifications and regulatory requirements, we plan to train and conduct quality certifications of each center as part of engagement. We intend for these qualified treatment centers to be the first and last points on our complex supply chain to reach patients in the commercial setting. We may not be able to engage qualified treatment centers in all of the regions in our commercial launch strategy, or we may encounter other challenges or delays in engaging qualified treatment centers. We may fail to manage the logistics of collecting and shipping patient material to the manufacturing site and shipping the product candidate back to the patient. Logistical and shipment delays and problems caused by us, our vendors other factors not in our control, such as weather, could prevent or delay the delivery of products to patients. If our qualified treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm. We anticipate having to maintain a complex chain of identity and chain of custody with respect to patient material as it moves through the manufacturing process, from the qualified treatment center to the transduction facility, and back to the patient. Failure to maintain chain of identity and chain of custody could adverse patient outcomes, loss of product or regulatory action.

*Although we are continuing to build out our field team, we have no sales or distribution experience and only early capabilities for marketing and market access, and expect to invest significant financial and management resources to establish these capabilities. If we are unable to establish sales and distribution capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenues.*

Although we are continuing to build out our field team in anticipation of our potential first commercial launch in Europe in 2019, we have no sales or distribution experience and only early capabilities for marketing and market access. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities in the United States, Europe and other regions, either on our own or with others. We may enter into collaborations with other entities to utilize their mature marketing and distribution capabilities, but we may be unable to enter into marketing agreements on favorable terms, if at all. If our future collaborative partners do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without a significant internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

*We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates. If our competitors obtain orphan drug exclusivity for products that regulatory authorities determine constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.*

We are engaged in gene therapy for severe genetic diseases and cancer, both of which are competitive and rapidly changing fields. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, manufacturing capabilities, experienced marketing and manufacturing organizations. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective, safer, or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than us. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors. For additional information regarding our competition, see "Item 1. Business-Competition" in our Annual Report.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products. If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

In addition, although our product candidates have been granted orphan drug status by the FDA and EMA, there are limitations to the exclusivity. In the United States, the exclusivity period for orphan drugs is seven years, while pediatric exclusivity adds six months to any existing patents or exclusivity periods. In Europe, orphan drugs may be able to obtain 10 years of marketing exclusivity and up to an additional two years on the basis of qualifying pediatric studies. However, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria. Additionally, a marketing authorization holder may lose its orphan exclusivity if it consents to a second orphan drug application or cannot supply enough drug. Orphan drug exclusivity also can be lost when a second applicant demonstrates its drug is "clinically superior" to the original orphan drug. Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the exclusivity period for the applicable indication.

Finally, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

***The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.***

Ethical, social and legal concerns about gene therapy and genetic research could result in additional regulations restricting or prohibiting the products and processes we may use. Even with the requisite approvals, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party or governmental payors accepting gene therapy products in general, and our product candidates in particular, as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the chemotherapy and myeloablative treatments associated with the procedure by which our product candidates are administered;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- the pricing of our products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. For instance, UniQure encountered challenges in commercializing Glybera, the first approved gene therapy in Europe, and did not seek renewal of Glybera's marketing authorization in Europe when it expired in October 2017, due to forecasted patient demand and limited use since its approval in 2012. Our efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors.

***We intend to market our products outside of the United States, and we will be subject to the risks of doing business outside of the United States.***

Because we intend to market our product candidates, if approved, outside of the United States, our business is subject to risks associated with doing business outside of the United States. Accordingly, our business and financial results in the future could be adversely affected due to a variety of factors, including:

- efforts to develop an international sales, marketing and distribution organization may increase our expenses, divert our management's attention from the acquisition or development of product candidates or cause us to forgo profitable licensing opportunities in these geographies;
- changes in a specific country's or region's political and cultural climate or economic condition;
- unexpected changes in foreign laws and regulatory requirements;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- inadequate intellectual property protection in foreign countries;
- trade-protection measures, import or export licensing requirements such as Export Administration Regulations promulgated by the U.S. Department of Commerce and fines, penalties or suspension or revocation of export privileges;
- the effects of applicable foreign tax structures and potentially adverse tax consequences; and
- significant adverse changes in foreign currency exchange rates.

In addition to FDA and related regulatory requirements in the United States and abroad, we are subject to extensive additional federal, state and foreign anti-bribery regulation, which include the U.S. Foreign Corrupt Practices Act, the U.K. Bribery Act, and similar laws in other countries outside of the United States. We have developed and implemented a corporate compliance program based on what we believe are current best practices in the pharmaceutical industry for companies similar to ours, but we cannot guarantee that we, our employees, our consultants or our third-party contractors are or will be in compliance with all federal, state and foreign regulations regarding bribery and corruption. Moreover, our partners and third party contractors located outside the United States may have inadequate compliance programs or may fail to respect the laws and guidance of the territories in which they operate. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could also have an adverse effect on our business, financial condition and results of operations.

*The insurance coverage and reimbursement status of newly-approved products is uncertain. Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face additional uncertainty related to pricing and reimbursement for our product candidates. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.*

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as our gene therapy products. In addition, because our therapies represent new treatment approaches, the estimation of potential revenues will be complex. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, including gene therapies that are potential one-time treatments. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. A number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries. In addition, costs or difficulties with the reimbursement experienced by the initial gene therapies to receive marketing authorization may create an adverse environment for reimbursement of other gene therapies.

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these foreign jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

Moreover, increasing efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Furthermore, because our target patient populations are relatively small, the pricing and reimbursement of our product candidates, if approved, must be adequate to support our commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. We have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as our LentiGlobin product candidate. While we are engaged in discussions with potential payors, there is no assurance that any payors will adopt these payment models. Even with these payment models, there may be substantial resistance to the cost of our products by payors and the public generally. These payment models may not be sufficient for payors to grant coverage, and if we are unable to obtain adequate coverage for our products, the adoption of our products may be limited. In addition, to the extent reimbursement for our products is subject to outcomes-based arrangements, our future cash collection and revenues from product sales will be at risk. Moreover, the administration of our products require procedures for the collection of HSCs from the patient, followed by chemotherapy and myeloablative treatments, before infusion of the engineered cell therapy product. The manner and level at which reimbursement is provided for these services is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products. These factors could affect our ability to successfully commercialize our products and generate revenues, which would adversely impact our business, financial condition, results of operations and prospects.

***Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.***

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the Affordable Care Act, was passed, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (70% commencing January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since January 2017, the Trump administration has signed two Executive Orders designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. One Executive Order directs federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in Affordable Care Act risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the Affordable Care Act marketplace, providers, and potentially our business, are not yet known.

In July 2018, the CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act-qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS has recently published a final rule that would give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the Affordable Care Act for plans sold through such marketplaces. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the Tax Cuts and Jobs Act of 2017, the remaining provisions of the Affordable Care Act are invalid as well. While the Trump Administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the Texas District Court Judge issued an order staying the judgment pending appeal, it is unclear how this decision, subsequent appeals and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

Since its enactment, some of the provisions of the Affordable Care Act have yet to be fully implemented, while certain provisions have been subject to judicial, congressional, or executive challenges. As a result, there have been delays in the implementation of, and action taken to repeal or replace, certain aspects of the Affordable Care Act. The U.S. Supreme Court has upheld certain key aspects of the legislation, including a tax-based shared responsibility payment imposed on certain individuals who fail to maintain qualifying health coverage for all or part of a year or pay a penalty, which is commonly known as the “individual mandate.” However, as a result of tax reform legislation passed in December 2017, the individual mandate has been eliminated effective January 1, 2019. On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amends the Affordable Care Act, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.”

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation’s automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2025 unless Congress takes additional action. These reductions were extended through 2027 under the BBA. In January 2013, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration’s budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump administration released a “Blueprint” to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private third-party payors.

The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

***If the market opportunities for our product candidates are smaller than we believe they are, and if we are not able to successfully identify patients and achieve significant market share, our revenues may be adversely affected and our business may suffer.***

We focus our research and product development on treatments for severe genetic diseases and cancer. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower or more difficult to identify than expected. For instance, because newborn screening for CALD is not widely adopted, and it can be difficult to diagnose CALD in the absence of a genetic screen, we may have difficulty finding patients who would benefit from treatment from our Lenti-D product candidate. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. For instance, we are initially seeking approval of our LentiGlobin product candidate for the treatment of patients with TDT and non- $\beta$ 0/ $\beta$ 0 genotypes. We do not have any assurance whether or when the LentiGlobin product candidate may be commercially available to patients with all genotypes of TDT.

Even if we obtain significant market share for our product candidates within an approved indication, because the potential target populations for our product candidates are small, we may never achieve profitability without obtaining regulatory approval for additional indications. For instance, in the field of cancer, the FDA often approves new therapies initially only for use in patients with relapsed or refractory advanced disease. We expect to initially seek approval of our T cell-based product candidates in cancer in this context. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval in earlier lines of treatment and potentially as a first line therapy, but there is no guarantee that our product candidates, even if approved, would be approved for earlier lines of therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

Any of these factors may negatively affect our ability to generate revenues from sales of our product and our ability to achieve and maintain profitability, and as a consequence, our business may suffer.

**Risks related to our business operations**

***If we undertake business combinations, collaborations or similar strategic transactions, they may disrupt our business, divert management's attention, dilute stockholder value or be difficult to integrate.***

On a regular basis, we consider various business combination transactions, collaborations, license agreements and strategic transactions with third parties, including transactions which may result in us acquiring, or being acquired by, a third party. The consummation or performance of any future business combination, collaboration or strategic transaction may involve risks, such as:

- diversion of managerial resources from day-to-day operations;
- challenges associated with integrating acquired technologies and operations of acquired companies;
- exposure to unforeseen liabilities;
- difficulties in the assimilation of different cultures and practices, as well as in the assimilation and retention of broad and geographically dispersed personnel and operations;
- misjudgment with respect to value, return on investment or strategic fit;
- higher than expected transaction costs; and
- additional dilution to our existing stockholders if we issue equity securities as consideration for any acquisitions.

As a result of these risks, we may not be able to achieve the expected benefits of any such transaction. If we are unsuccessful in completing or integrating any acquisition, we may be required to reevaluate that component of our strategy only after we have incurred substantial expenses and devoted significant management time and resources in seeking to complete and integrate the acquisition.

Future business combinations could involve the acquisition of significant intangible assets. We may need to record write-downs from future impairments of identified intangible assets and goodwill. These accounting charges would increase a reported loss or reduce any future reported earnings. In addition, we could use substantial portions of our available cash to pay the purchase price for company or product candidate acquisitions. Subject to the limitations under our existing indebtedness, it is possible that we could incur additional debt or issue additional equity securities as consideration for these acquisitions, which could cause our stockholders to suffer significant dilution.

***Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.***

Public perception may be influenced by claims that gene therapy, including gene editing technologies, is unsafe or unethical, and research activities and adverse events in the field, even if not ultimately attributable to us or our product candidates could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product candidates. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop.

***Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.***

We are highly dependent on principal members of our executive team and key employees, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are “at will” employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

***As we evolve from a U.S.-based company primarily involved in discovery, pre-clinical research and clinical development into a company that develops and commercializes multiple drugs with an international presence, we will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.***

We filed our first application for marketing authorization in 2018 and are preparing for a potential commercial launch in 2019, which we hope will be the first of a sequence of marketing approvals and commercial launches for multiple products across multiple geographies. As we advance multiple product candidates through late-stage clinical research and plan submissions for marketing authorizations, we are expanding our operations in the United States and Europe. We grew our workforce significantly during 2017 and 2018, and as of December 31, 2018, we had 745 full-time employees. As we pursue our development and commercialization strategy, we expect to expand our full-time employee base and to hire more consultants and contractors in the United States and Europe. This expected growth may place a strain on our administrative and operational infrastructure. As a result, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy.

***We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties, reputational harm, and diminished profits and future earnings.***

In the United States, the research, manufacturing, distribution, sale, and promotion of drugs and biologic products are subject to regulation by various federal, state, and local authorities in addition to FDA, including CMS, other divisions of the HHS, (e.g., the Office of Inspector General), the United States Department of Justice offices of the United States Attorney, the Federal Trade Commission and state and local governments. Our operations are directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations and equivalent provisions in other countries. These laws apply to, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business.

State and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. Most recently, the Bipartisan Budget Act of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute. Enforcement agencies also continue to pursue novel theories of liability under these laws. In particular, government agencies have recently increased regulatory scrutiny and enforcement activity with respect to programs supported or sponsored by pharmaceutical companies, including reimbursement and co-pay support, funding of independent charitable foundations and other programs that offer benefits for patients. Several investigations into these programs have resulted in significant civil and criminal settlements.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

In the EU, interactions between pharmaceutical companies, healthcare professionals, and patients are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct in the individual EU member states. The provision of benefits or advantages to healthcare professionals to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU. Also, direct-to-consumer advertising of prescription-only medicinal products is prohibited at the EU level and in the individual member states. In addition, the UK Bribery Act applies to any company incorporated in or "carrying on business" in the UK, irrespective of where in the world the alleged bribery activity occurs, which could have implications for our interactions with physicians both in and outside of the UK. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU member states must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU member states. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

EU member states, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is currently governed by the provisions of the General Data Protection Regulation, or the GDPR. The GDPR, together with the national legislation of the individual EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals for the consent to be considered valid, the transfer of personal data out of the European Economic Area, security breach notifications, the use of third-party processors in connection with the processing of the personal data, confidentiality of the personal data, as well as substantial potential fines for breaches of the data protection obligations. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR.

*We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.*

The use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients participating in clinical trials, consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical study participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance and we believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

*We may not be successful in our efforts to identify or discover additional product candidates.*

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our gene therapy and gene editing platforms. Our research programs, including our oncology research programs, may fail to identify other potential product candidates for clinical development for a number of reasons. We may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

***We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.***

Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

***Comprehensive tax reform legislation could adversely affect our business and financial condition.***

On December 22, 2017, the “Tax Cuts and Jobs Act” (TCJA) was enacted. The TCJA significantly reforms the Internal Revenue Code of 1986, as amended (the “Code”). The TCJA, among other things, includes changes to U.S. federal tax rates, imposes significant additional limitations on the deductibility of interest and net operating loss carryforwards, allows for the expensing of capital expenditures, and puts into effect the migration from a “worldwide” system of taxation to a territorial system. Our net deferred tax assets and liabilities have been revalued at the newly enacted U.S. corporate tax rate, and the impact of the reduction to our deferred tax assets and associated valuation allowance was recognized in 2017. We continue to examine the impact this tax reform legislation may have on our business. The impact of this tax reform is uncertain and could be adverse.

***The increasing use of social media platforms presents new risks and challenges.***

Social media is increasingly being used to communicate about our clinical development programs and the diseases our product candidates are being developed to treat. We intend to utilize appropriate social media in connection with our commercialization efforts following approval of our product candidates. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media channels to report an alleged adverse event. When such disclosures occur, there is a risk that we fail to monitor and comply with applicable adverse event reporting obligations, or we may not be able to defend our business or the public’s legitimate interests in the face of the political and market pressures generated by social media due to restrictions on what we may say about our investigational products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website, or a risk that a post on a social networking website by any of our employees may be construed as inappropriate promotion. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions, or incur other harm to our business.

***Our computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates’ development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.***

Our computer systems and those of our current or future third-party collaborators, service providers, contractors and consultants may fail and are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, service providers, contractors and consultants, and the large amounts of information stored on those systems make those systems vulnerable to service interruptions, security breaches, or other failures, resulting from inadvertent or intentional actions by our employees or those of third-party business partners, or from cyber-attacks by malicious third parties. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized groups and individuals with a wide range of motives and expertise. In addition to extracting sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The prevalent use of mobile devices also increases the risk of data security incidents. If we experience a material system failure, accident or security breach that causes interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in significant reputational, financial, legal, regulatory, business or operational harm. For example, the loss of clinical trial data for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. We also rely on third-party service providers for aspects of our internal control over financial reporting and such service providers may experience a material system failure or fail to carry out their obligations in other respects, which may impact our ability to produce accurate and timely financial statements, thus harming our operating results, our ability to operate our business, and our investors’ view of us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to material failures, security breaches, cyberattacks and other related breaches.

Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations to third parties, or any data security incidents or other security breaches that result in the unauthorized access, release or transfer of sensitive information, including personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us, could cause third parties to lose trust in us or could result in claims by third parties asserting that we have breached our privacy, confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents.

#### **Risks related to our intellectual property**

*If we are unable to obtain or protect intellectual property rights related to our product candidates, we may not be able to compete effectively in our markets.*

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. Several patent applications covering our product candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

***Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.***

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, *ex parte* reexaminations, post-grant review, and *inter partes* review proceedings before the U.S. Patent and Trademark Office, or U.S. PTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

***We may not be successful in obtaining or maintaining necessary rights to gene therapy product components and processes for our development pipeline through acquisitions and in-licenses.***

Presently we have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

For example, we sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

***If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.***

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In many cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

***We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.***

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

***We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.***

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

***We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.***

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We have had in the past, and we may also have to in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

***Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.***

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

***Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.***

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including patent eligible subject matter, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

***Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore obtaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

***We may not be able to protect our intellectual property rights throughout the world.***

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

**Risks related to ownership of our common stock**

***The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchase them.***

Companies trading in the stock market in general, and The NASDAQ Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and biotechnology and pharmaceutical industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

The market price of our common stock may be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical or clinical studies;
- reports of adverse events in other gene therapy products or clinical studies of such products;
- inability to obtain additional funding;
- any delay in filing an IND, MAA or BLA for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that IND, MAA or BLA;
- failure to successfully manage the commercial launch of our product candidates following regulatory approval, including failure to manage our supply chain operations in the coordination and delivery of drug product to patients at qualified treatment centers;
- failure to obtain sufficient pricing and reimbursement for our product candidates from private and governmental payors;
- failure to obtain market acceptance and adoption of our product;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

*Actual or potential sales of our common stock by our employees, including our executive officers, pursuant to pre-arranged stock trading plans could cause our stock price to fall or prevent it from increasing for numerous reasons, and actual or potential sales by such persons could be viewed negatively by other investors.*

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers and members of our board of directors, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing for numerous reasons.

*Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.*

Additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2013 Stock Option and Incentive Plan, or the 2013 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2013 Plan automatically increases each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2013 Plan each year. If our board of directors or compensation committee elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall. We also have an Employee Stock Purchase Plan and any shares of common stock purchased pursuant to that plan will also cause dilution.

***We could be subject to securities class action litigation.***

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

***Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.***

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We have completed several financings since our inception which we believe have resulted in a change in control as defined by IRC Section 382. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. The TCJA also reduced the corporate income tax rate to 21%, from a prior rate of 35%. This may cause a reduction in the economic benefit of our NOLs and other deferred tax assets available to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

***We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.***

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

*Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.*

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

#### **Item 1B. Unresolved Staff Comments**

Not applicable.

#### **Item 2. Properties**

Our corporate headquarters are located in Cambridge, Massachusetts. Our current leased facility encompasses approximately 253,108 square feet of office and laboratory space, located at 60 Binney Street, Cambridge, Massachusetts. The lease commenced on October 1, 2016 and will continue until March 31, 2027. We have the option to extend the 60 Binney Street lease for two successive five-year terms. We also lease approximately 7,800 square feet of office and laboratory space in Seattle, Washington. We entered into a new lease agreement for 36,000 square feet of office and laboratory space in Seattle, Washington in July 2018, with the anticipated move-in date in mid-2019. The new lease will continue for approximately 8 years following the commencement date of the lease in January 2019. In November 2017, we purchased a 125,000 square foot manufacturing facility located in Durham, North Carolina to provide manufacturing capacity for lentiviral vector in support of our current and planned gene and cell therapies. We also lease office space in Zug, Switzerland, the location of our European headquarters, and entered into a new lease agreement in September 2018 for 1,136 square meters of office space. The new Zug lease will continue for 60 months with the option to renew for 2 successive 60 month terms. We believe that our existing facilities are adequate for our current needs.

**Item 3. Legal Proceedings**

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements, employment and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of December 31, 2018, we were not party to any legal or arbitration proceedings that may have, or have had in the recent past, significant effects on our financial position or profitability. We believe no governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

**Item 4. Mine Safety Disclosures**

Not applicable.

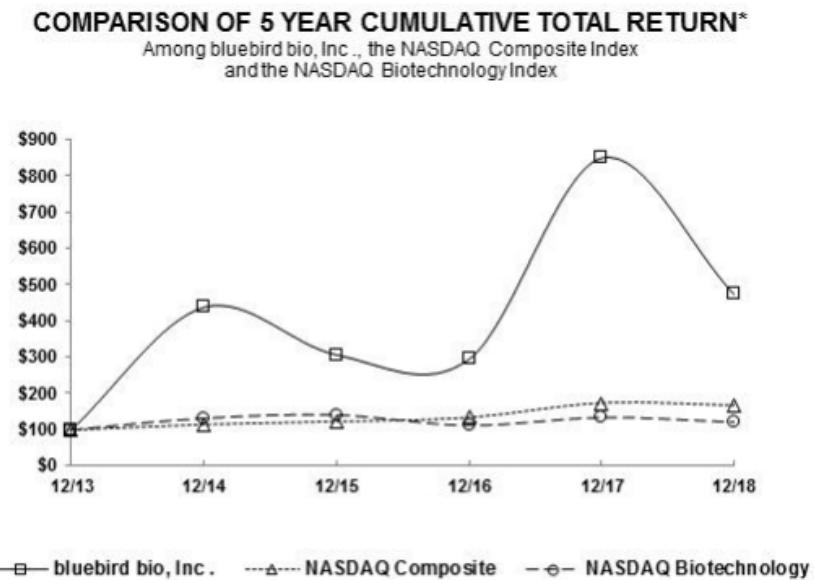
**PART II****Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities**

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE." On February 15, 2019, the last reported sale price for our common stock on the Nasdaq Global Select Market was \$137.03 per share.

**Stock Performance Graph**

The graph set forth below compares the cumulative total stockholder return on our common stock between June 19, 2013 (the date of our initial public offering) and December 31, 2018, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of \$100 on June 19, 2013 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The graph assumes our closing sales price on June 19, 2013 of \$26.91 per share as the initial value of our common stock and not the initial offering price to the public of \$17.00 per share.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.



\*\$100 invested on 12/31/13 in stock or index, including reinvestment of dividends.  
Fiscal year ending December 31.

**Holders**

As of February 15, 2019, there were approximately 8 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

**Dividends**

We have not paid any cash dividends on our common stock since inception and do not anticipate paying cash dividends in the foreseeable future.

**Securities Authorized for Issuance Under Equity Compensation Plans**

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

**Item 6. Selected Financial Data**

The following selected consolidated financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations", the consolidated financial statements and related notes, and other financial information included in this Annual Report on Form 10-K.

We derived the consolidated financial data for the years ended December 31, 2018, 2017 and 2016 and as of December 31, 2018 and 2017 from our audited consolidated financial statements, which are included elsewhere in this Annual Report on Form 10-K. We derived the consolidated financial data for the years ended December 31, 2015 and 2014 and as of December 31, 2016, 2015 and 2014 from our audited consolidated financial statements that are not included elsewhere in this Annual Report on Form 10-K. Historical results are not necessarily indicative of the results to be expected in future periods.

	Year ended December 31,				
	2018 (1)	2017	2016	2015	2014
	(in thousands, except per share amounts)				
<b>Consolidated statements of operations data:</b>					
Revenue:					
Collaboration revenue	\$ 52,353	\$ 22,207	\$ 6,155	\$ 14,079	\$ 25,031
License and royalty revenue	2,226	13,220	-	-	390
Total revenues	<u>54,579</u>	<u>35,427</u>	<u>6,155</u>	<u>14,079</u>	<u>25,421</u>
Operating expenses:					
Research and development	448,589	273,040	204,775	134,038	62,574
General and administrative	174,129	93,550	65,119	46,209	23,227
Cost of license and royalty revenue	885	1,527	-	-	-
Change in fair value of contingent consideration	2,999	(525 )	4,091	2,869	246
Total operating expenses	<u>626,602</u>	<u>367,592</u>	<u>273,985</u>	<u>183,116</u>	<u>86,047</u>
Loss from operations	(572,023 )	(332,165 )	(267,830 )	(169,037 )	(60,626 )
Interest income (expense), net	14,624	(2,001 )	3,782	1,591	290
Other income (expense), net	1,961	(1,267 )	(71 )	723	(170 )
Income tax benefit (expense)	(187 )	(210 )	612	(60 )	11,797
Net loss	<u>\$ (555,625 )</u>	<u>\$ (335,643 )</u>	<u>\$ (263,507 )</u>	<u>\$ (166,783 )</u>	<u>\$ (48,709 )</u>
Net loss per share - basic and diluted	<u>\$ (10.68 )</u>	<u>\$ (7.71 )</u>	<u>\$ (7.07 )</u>	<u>\$ (4.81 )</u>	<u>\$ (1.83 )</u>
Weighted-average number of common shares used in net loss per share - basic and diluted	<u>52,032</u>	<u>43,535</u>	<u>37,284</u>	<u>34,669</u>	<u>26,546</u>

(1) Effective January 1, 2018, we adopted Accounting Standards Codification, Topic 606, Revenue from Contracts with Customers ("Topic 606"). For further information regarding the adoption of Topic 606 and the impact on our consolidated financial

statements, refer to Note 2, "Summary of significant accounting policies and basis of presentation", to the accompanying consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

	As of December 31,				
	2018	2017	2016 (in thousands)	2015	2014
<b>Consolidated balance sheet data:</b>					
Cash, cash equivalents and marketable securities	\$ 1,891,427	\$ 1,614,302	\$ 884,830	\$ 865,763	\$ 492,003
Total assets	2,242,844	1,900,567	1,118,122	1,002,337	556,739
Total current liabilities	146,431	95,612	74,533	40,368	42,978
Financing lease obligation, net of current portion	153,319	154,749	120,140	61,901	-
Other long-term obligations	58,024	26,774	54,009	49,572	22,504
<b>Total stockholders' equity</b>	<b>\$ 1,885,070</b>	<b>\$ 1,623,432</b>	<b>\$ 869,440</b>	<b>\$ 850,496</b>	<b>\$ 491,257</b>

## **Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations**

*The following information should be read in conjunction with the consolidated financial statements and related notes thereto included in this Annual Report on Form 10-K.*

*In addition to historical information, this report contains forward-looking statements that involve risks and uncertainties which may cause our actual results to differ materially from plans and results discussed in forward-looking statements. We encourage you to review the risks and uncertainties discussed in the sections entitled Item 1A. "Risk Factors" and "Forward-Looking Statements" included at the beginning of this Annual Report on Form 10-K. The risks and uncertainties can cause actual results to differ significantly from those forecast in forward-looking statements or implied in historical results and trends.*

*We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.*

### **Overview**

We are a clinical-stage biotechnology company committed to developing potentially transformative gene therapies for severe genetic diseases and cancer. With our lentiviral-based gene therapy and gene editing capabilities, we have built an integrated product platform with broad therapeutic potential in a variety of indications. We believe that gene therapy for severe genetic diseases has the potential to change the way these patients are treated by correcting the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. Our clinical programs in severe genetic diseases include our LentiGlobin® product candidate as a treatment for each of transfusion-dependent β-thalassemia, or TDT, and severe sickle cell disease, or SCD, and our Lenti-D™ product candidate as a treatment for cerebral adrenoleukodystrophy, or CALD, a rare hereditary neurological disorder. Our programs in oncology are built upon our leadership in lentiviral gene delivery and T cell engineering, with a focus on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. bb2121 and bb21217, our product candidates in oncology, are CAR T cell product candidates for the treatment of multiple myeloma.

In October 2018, we announced that the European Medicines Agency, or EMA, has accepted for review our marketing authorization application, or MAA, of our LentiGlobin product candidate for the treatment of adult and adolescent patients with TDT and non-β0/β0 genotypes. We expect to launch LentiGlobin in Europe and begin to generate product revenues, if we receive conditional approval, in 2019. We plan to file a biologics license application, or BLA, in the United States in 2019 for the use of LentiGlobin in the treatment of adult and adolescent patients with TDT and non-β0/β0 genotypes. We are also engaged with the U.S. Food and Drug Administration, or FDA, and the EMA in discussions regarding our proposed development plans for LentiGlobin in SCD, with a potential first submission for regulatory approval in 2022.

If our Lenti-D product candidate shows a sufficiently compelling treatment effect, and pending further discussion with regulatory authorities, the results from our Starbeam study could potentially form the basis of a Biologics License Application, or BLA, and a Marketing Authorization Application, or MAA, submission in the United States and European Union, respectively. We anticipate a potential first submission for regulatory approval of our Lenti-D product candidate for the treatment of patients with CALD in 2019.

In collaboration with Celgene Corporation, or Celgene, we are developing our bb2121 and bb21217 product candidates in multiple myeloma, a hematologic malignancy that develops in the bone marrow and is fatal if untreated. We are co-developing and co-promoting the bb2121 product candidate in the United States with Celgene and we have exclusively licensed to Celgene the development and commercialization rights for the bb2121 product candidate outside of the United States. We and Celgene anticipate the first potential approval of the bb2121 product candidate for the treatment of relapsed and refractory multiple myeloma in 2020. We have exclusively licensed the development and commercialization rights for the bb21217 product candidate to Celgene, with an option for us to elect to co-develop and co-promote bb21217 within the United States.

As of December 31, 2018, we had cash, cash equivalents and marketable securities of approximately \$1.9 billion. We expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our current planned operations into 2022.

Since our inception in 1992, we have devoted substantially all of our resources to our development efforts relating to our product candidates, including activities to manufacture product candidates in compliance with good manufacturing practices, or GMP, to conduct clinical studies of our product candidates, to provide general and administrative support for these operations and to protect our intellectual property. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations primarily through the sale of common stock in our public offerings, private placements of preferred stock and warrants and through collaborations.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were \$555.6 million for the year ended December 31, 2018 and our accumulated deficit was \$1.5 billion as of December 31, 2018. Substantially all our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing and planned activities, as we:

- conduct clinical studies for our LentiGlobin and Lenti-D product candidates, as well as to fund our share of the costs of clinical studies for the bb2121 and bb21217 product candidates partnered with Celgene;
- increase research and development-related activities for the discovery and development of oncology product candidates;
- continue our research and development efforts internally and through our collaborations with external partners, such as with Regeneron;
- manufacture clinical study materials and establish the infrastructure necessary to support and develop large-scale manufacturing capabilities;
- seek regulatory approval for our product candidates;
- add personnel to support our product development and commercialization efforts; and
- increase activities leading up to the potential commercial launch of our LentiGlobin and Lenti-D product candidates.

We do not expect to generate any product revenues until the second half of 2019, assuming we receive marketing approval for LentiGlobin. While we are in the process of building out our internal lentiviral vector manufacturing capacity, currently all of our manufacturing activities are contracted out to third parties. Additionally, we currently utilize third-party contract research organizations, or CROs, to carry out our clinical development activities. As we seek to obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses as we prepare for product sales, marketing, manufacturing, and distribution. Accordingly, we will seek to fund our operations through public or private equity or debt financings, strategic collaborations, or other sources. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our products.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenues from the sale of our products, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

## **Financial operations overview**

### **Revenue**

To date, we have not generated any revenues from the sale of products. Our revenues have been derived from collaboration arrangements, out-licensing arrangements, research fees, and grant revenues. Effective January 1, 2018, we adopted Accounting Standards Codification (“ASC”), Topic 606, *Revenue from Contracts with Customers* (“Topic 606”), using the modified retrospective transition method.

To date, our collaboration revenue has been primarily generated from our collaboration arrangement with Celgene Corporation (“Celgene”), which was originally entered into in March 2013 and was subsequently amended in June 2015, as further described in Note 10, “*Collaborative arrangements*”. The terms of the arrangement with respect to bb2121 contain multiple promised goods or services, which include: (i) research and development services, (ii) a license to bb2121, and (iii) manufacture of vectors and associated payload for incorporation into bb2121 under the license. As of September 2017, the Celgene collaboration also included the following promised goods or services with respect to bb21217: (i) research and development services, (ii) a license to bb21217, and (iii) manufacture of vectors and associated payload for incorporation into bb21217 under the license. In March 2018, we entered into an agreement with Celgene to co-develop and co-promote bb2121 in which both parties will share equally in U.S. costs and profits.

In August 2018, we entered in a collaboration arrangement with Regeneron Pharmaceuticals, Inc (“Regeneron”). We began recognizing collaboration revenue under this arrangement in the fourth quarter of 2018.

Nonrefundable license fees are recognized as revenue upon delivery of the license provided there are no unsatisfied performance obligations in the arrangement. License revenue has historically been generated from our out-license agreements with Novartis Pharma AG, or Novartis, and GlaxoSmithKline Intellectual Property Development Limited, or GSK. The license agreement with GSK was assigned by GSK to Orchard Therapeutics Limited, or Orchard, effective as of April 11, 2018. Under our out-licensing agreements we may also recognize revenue from potential future milestone payments and royalties.

Please refer to Note 2, “*Summary of significant accounting policies and basis of presentation*” in the Notes to Consolidated Financial Statements, for further information for further discussion of our accounting policies.

#### ***Research and development expenses***

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with CROs and clinical sites that conduct our clinical studies;
- costs of acquiring, developing, and manufacturing clinical study materials;
- reimbursable costs to our partners for collaborative activities;
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, information technology, insurance, and other supplies in support of research and development activities;
- costs associated with our research platform and preclinical activities;
- milestones and upfront license payments;
- costs associated with our regulatory, quality assurance and quality control operations; and
- amortization of intangible assets.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. The duration, costs, and timing of clinical studies and development of our product candidates will depend on a variety of factors, any of which could mean a significant change in the costs and timing associated with the development of our product candidates including:

- the scope, rate of progress, and expense of our ongoing as well as any additional clinical studies and other research and development activities we undertake;
- future clinical study results;
- uncertainties in clinical study enrollment rates;
- changing standards for regulatory approval; and
- the timing and receipt of any regulatory approvals.

We plan to increase our research and development expenses for the foreseeable future as we continue to advance the development of our Lenti-D, LentiGlobin, bb2121, and bb21217 product candidates, conduct research and development activities in oncology, including under our strategic collaborations with Celgene and Regeneron, and continue the research and development of product candidates using our gene editing technology platform. Our research and development expenses include expenses associated with the following activities:

- Northstar-2 Study (HGB-207) - a multi-site, international phase 3 study to examine the safety and efficacy of our LentiGlobin product candidate in the treatment of patients with TDT and a non- $\beta$ 0/ $\beta$ 0 genotype.
- Northstar-3 Study (HGB-212) - a multi-site, international phase 3 study to examine the safety and efficacy of our LentiGlobin product candidate in the treatment of patients with TDT and a  $\beta$ 0/ $\beta$ 0 genotype or an IVS-I-110 mutation.
- HGB-205 study - a single-center phase 1/2 study in France to study the safety and efficacy of our LentiGlobin product candidate in the treatment of subjects with TDT and of patients with SCD.

- HGB-206 study - a multi-site phase 1/2 study in the United States to study the safety and efficacy of our LentiGlobin product candidate in the treatment of patients with SCD.
- Our planned HGB-210 study - our planned multi-site, international phase 3 study of patients with SCD and a history of vaso-occlusive events. We plan to initiate this study in 2019.
- Starbeam Study (ALD-102) - a multi-site, international phase 2/3 study to examine the safety and efficacy of our Lenti-D product candidate in the treatment of patients with CALD.
- Our planned ALD-104 study - our planned multi-site phase 3 study to examine the safety and efficacy of our Lenti-D product candidate in the treatment of patients with CALD.
- CRB-401 study - an open label, single-arm, multi-center, phase 1 study to examine the safety and efficacy of the bb2121 product candidate in the treatment of patients with relapsed and refractory multiple myeloma.
- CRB-402 study - an open label, single-arm, multicenter, phase 1 study to examine the safety and efficacy of the bb21217 product candidate in the treatment of patients with relapsed and refractory multiple myeloma.
- Additional planned clinical studies for the development of bb2121, including: KarMMA-2 (MM-002), the planned multi-cohort, open-label, multicenter phase 2 study to examine the safety and efficacy of the bb2121 product candidate in the treatment of patients with relapsed and refractory multiple myeloma and in high-risk multiple myeloma; KarMMA-3 (MM-003), the planned multicenter, randomized, open-label phase 3 study comparing the efficacy and safety of the bb2121 product candidate versus standard triplet regimens in patients with relapsed and refractory multiple myeloma; and a planned multi-center phase 2 study to examine the safety and efficacy of the bb2121 product candidate in the treatment of patients with newly-diagnosed multiple myeloma.
- We will continue to manufacture clinical study materials in support of our clinical studies.

From inception through December 31, 2018, we have incurred \$1.2 billion in research and development expenses. Our direct research and development expenses consist principally of external costs, such as fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical studies, license and milestone fees, and costs related to acquiring and manufacturing clinical study materials. We allocate salary and benefit costs directly related to specific programs. We do not allocate personnel-related discretionary bonus or stock-based compensation costs, costs associated with our general discovery platform improvements, depreciation or other indirect costs that are deployed across multiple projects under development and, as such, the costs are separately classified as other research and development expenses in the table below:

	Year ended December 31,		
	2018	2017 (in thousands)	2016
LentiGlobin	\$ 125,058	\$ 85,710	\$ 67,154
Lenti-D	38,244	16,223	18,612
bb2121	75,667	32,144	12,690
bb21217	15,624	7,402	-
Pre-clinical programs	50,115	40,167	32,771
Total direct research and development expense	304,708	181,646	131,227
Employee- and contractor-related expenses	35,697	23,698	17,047
Stock-based compensation expense	54,422	26,633	19,690
Platform-related expenses	18,187	15,414	15,359
Facility expenses	32,158	24,700	20,301
Other expenses	3,417	949	1,151
Total other research and development expenses	143,881	91,394	73,548
<b>Total research and development expense</b>	<b>\$ 448,589</b>	<b>\$ 273,040</b>	<b>\$ 204,775</b>

The costs associated with our bb21217 program were included in pre-clinical programs in the table shown above through June 30, 2017. The costs associated with our bb21217 program are presented separately in the table above beginning in the third quarter of 2017 as we initiated the first clinical study for bb21217 in the third quarter of 2017.

#### ***General and administrative expenses***

General and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses for our employees in executive, operational, finance, legal, business development, commercial, information technology, and human resource functions. Other general and administrative expenses include facility-related costs, professional fees for accounting, tax, legal and consulting services, directors' fees and expenses associated with obtaining and maintaining patents.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and the potential commercialization of our product candidates on a global basis. Additionally, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidates.

#### ***Cost of license and royalty revenue***

Cost of license and royalty revenue represents expense associated with amounts owed to third party licensors as a result of revenue recognized under our out-license arrangements with Novartis and Orchard.

We anticipate that our cost of license and royalty revenue will increase in the future contingent upon the achievement of regulatory milestones by Novartis or Orchard. Additionally, we anticipate that our cost of license and royalty revenue will increase in the future as we expect to continue to recognize royalty revenue related to Novartis' commercial sale of Kymriah.

#### ***Change in fair value of contingent consideration***

On June 30, 2014, we acquired Precision Genome Engineering, Inc., or Pregen. The agreement provided for up to \$135.0 million in future contingent cash payments by us upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregen technology.

As of December 31, 2018, there are \$120.0 million in future contingent cash payments, of which \$20.1 million relates to clinical milestones and \$99.9 million relates to commercial milestones. We estimate future contingent cash payments have a fair value of \$5.2 million as of December 31, 2018, all of which is classified as a non-current liability on our consolidated balance sheet.

#### ***Interest income (expense), net***

Interest income (expense), net consists primarily of interest income earned on investments and interest expense on the financing obligation for our headquarters at 60 Binney Street in Cambridge, Massachusetts.

#### ***Other income (expense), net***

Other income (expense), net consists primarily of unrealized gains on equity securities, gains and losses on the disposal of fixed assets, realized gains and losses on debt securities, and gains and losses on foreign currency transactions.

#### ***Critical accounting policies and significant judgments and estimates***

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the U.S. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. In making estimates and judgments, management employs critical accounting policies.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this annual report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

### **Revenue recognition**

#### *Revenue recognition*

Effective January 1, 2018, we adopted Accounting Standards Codification (“ASC”), Topic 606, *Revenue from Contracts with Customers* (“Topic 606”), using the modified retrospective transition method. Under this method, we have recognized the cumulative effect of the adoption as an adjustment to the opening balance of accumulated deficit in the current period consolidated balance sheet. We have not revised our consolidated financial statements for prior periods. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer’s discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations. The identification of material rights requires judgments related to the determination of the value of the underlying license relative to the option exercise price, including assumptions about technical feasibility and the probability of developing a candidate that would be subject to the option rights. The exercise of a material right is accounted for as a contract modification for accounting purposes.

We assess whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity’s promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, we consider factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. We also consider the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices (“SSP”) on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, we consider applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. We validate the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, we estimate the amount of consideration to which we will be entitled in exchange for transferring the promised goods or services to a customer. We determine the amount of variable consideration by using the expected value method or the most likely amount method. We include the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee’s control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, we adjust consideration for the effects of the time value of money if the timing of payments provides us with a significant benefit of financing. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. We assessed each of our revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of our arrangements.

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

#### *Collaboration revenue*

To date, collaboration revenue has been primarily generated from our collaboration arrangement with Celgene, which was originally entered into in March 2013 and was subsequently amended in June 2015, as further described in Note 10, “*Collaborative arrangements*”. In August 2018, we entered into a collaboration arrangement with Regeneron, and began recognizing collaboration revenue under this arrangement in the fourth quarter of 2018.

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements (“ASC 808”)* to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. Amounts that are owed to collaboration partners are recognized as an offset to collaboration revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed our collaboration revenues in each quarterly period, such amounts are classified as research and development expense. For those elements of the arrangement that are accounted for pursuant to Topic 606, we apply the five-step model described above.

#### *Impact of Topic 606 adoption*

As a result of adopting Topic 606, we recorded a \$29.4 million adjustment to the opening balance of accumulated deficit in the first quarter of 2018 primarily as a result of the accounting for the up-front consideration received in March 2013 in connection with the collaboration arrangement with Celgene under ASC 605-25 versus Topic 606. Refer below for a summary of the amount by which each financial statement line item was affected by the impact of the cumulative adjustment:

(in thousands)	Impact of Topic 606 adoption on consolidated balance sheet as of January 1, 2018			Balances without adoption of Topic 606
	As reported under Topic 606	Adjustments		
Deferred revenue, current portion	\$ 45,344	\$ 19,670		\$ 25,674
Deferred revenue, net of current portion	\$ 31,468	\$ 9,705		\$ 21,763
Accumulated deficit	\$ (943,183 )	\$ (29,375 )		\$ (913,808 )

The amount by which each financial statement line item is affected in the current reporting period by Topic 606 as compared with the guidance that was in effect prior to adoption is disclosed below.

<b>Impact of Topic 606 adoption on consolidated balance sheet as of December 31, 2018</b>			
(in thousands)	<b>As reported under Topic 606</b>	<b>Adjustments</b>	<b>Balances without adoption of Topic 606</b>
Deferred revenue, current portion	\$ 18,602	\$ 7,772	\$ 10,830
Deferred revenue, net of current portion	\$ 16,338	\$ 3,094	\$ 13,244
Accumulated deficit	\$ (1,498,808 )	\$ (10,866 )	\$ (1,487,942 )
<b>Impact of Topic 606 adoption on consolidated statement of operations and comprehensive loss for the twelve months ended December 31, 2018</b>			
(in thousands, except per share data)	<b>As reported under Topic 606</b>	<b>Adjustments</b>	<b>Balances without adoption of Topic 606</b>
Collaboration revenue	\$ 52,353	\$ 13,917	\$ 38,436
Research and development expense	\$ 448,589	\$ (4,592 )	\$ 453,181
Net loss	\$ (555,625 )	\$ 18,509	\$ (574,134 )
Net loss per share - basic and diluted:	\$ (10.68 )	\$ 0.35	\$ (11.03 )
<b>Impact of Topic 606 adoption on consolidated statement of cash flows for the twelve months ended December 31, 2018</b>			
(in thousands)	<b>As reported under Topic 606</b>	<b>Adjustments</b>	<b>Balances without adoption of Topic 606</b>
Net loss	\$ (555,625 )	\$ 18,509	\$ (574,134 )
Changes in deferred revenue	\$ (41,872 )	\$ (18,509 )	\$ (23,363 )

#### ***Financing lease obligation***

Beginning in 2015 through construction completion in 2017, we recorded certain estimated construction costs incurred and reported to us by the landlord for our corporate headquarters building, located at 60 Binney Street in Cambridge, Massachusetts, as an asset and corresponding construction financing lease obligation on our consolidated balance sheets because we were deemed to be the owner of the building during the construction period for accounting purposes. During construction, we periodically met with the landlord and its construction manager to review these estimates and observe construction progress before recording such amounts. Upon completion of the construction of the building in the first quarter of 2017, we evaluated the lease and determined that it did not meet the criteria for "sale-leaseback" treatment. Accordingly, we are depreciating the building over 40 years and incurring interest expense in our consolidated statement of operations and comprehensive loss related to the financing lease obligation recorded on our consolidated balance sheet. Any costs incurred by us that have been reimbursed by the landlord or that qualify for reimbursement by the landlord are recorded as an asset and financing lease obligation. Any incremental costs incurred directly by us that do not qualify for reimbursement by the landlord are also capitalized. We began occupying our corporate headquarters building on March 27, 2017.

#### ***Accrued research and development expenses***

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to development, manufacturing, and distribution of clinical trial materials.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period and adjust accordingly.

#### ***Stock-based compensation***

We issue stock-based awards to employees and non-employees, generally in the form of stock options and restricted stock units. We account for our stock-based awards in accordance with FASB ASC Topic 718, *Compensation-Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. Prior to the adoption of Accounting Standards Update (“ASU”) No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After the adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award. Stock-based compensation costs for non-employees are recognized as expense over the vesting period on a straight-line basis.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees, non-employees, and directors, with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. We estimate the probability that certain performance criteria will be met and do not recognize compensation expense until it is probable that the performance-based vesting condition will be achieved.

We estimate the fair value of our stock-based awards to employees, non-employees, and directors, using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of company specific historical and implied volatility data, we based our estimate of expected volatility on the estimate and expected volatilities of a representative group of publicly traded companies. For these analyses, we select companies with comparable characteristics to ours including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected life of our employee stock options using the “simplified” method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

#### ***Recent accounting pronouncements***

See Note 2 to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our business.

**Results of Operations*****Comparison of the years ended December 31, 2018 and 2017:***

	<b>Year ended December 31,</b>		<b>Change</b>
	<b>2018</b>	<b>2017</b>	
	<b>(in thousands)</b>		
<b>Revenue:</b>			
Collaboration revenue	\$ 52,353	\$ 22,207	\$ 30,146
License and royalty revenue	2,226	13,220	(10,994 )
Total revenues	54,579	35,427	19,152
<b>Operating expenses:</b>			
Research and development	448,589	273,040	175,549
General and administrative	174,129	93,550	80,579
Cost of license and royalty revenue	885	1,527	(642 )
Change in fair value of contingent consideration	2,999	(525 )	3,524
Total operating expenses	626,602	367,592	259,010
Loss from operations	(572,023 )	(332,165 )	239,858
Interest income (expense), net	14,624	(2,001 )	(16,625 )
Other income (expense), net	1,961	(1,267 )	(3,228 )
Loss before income taxes	(555,438 )	(335,433 )	220,005
Income tax expense	(187 )	(210 )	(23 )
Net loss	<u>\$ (555,625 )</u>	<u>\$ (335,643 )</u>	<u>\$ 219,982</u>

**Revenue.** Total revenue was \$54.6 million for the year ended December 31, 2018, compared to \$35.4 million for the year ended December 31, 2017. The increase of \$19.2 million was primarily attributable to collaboration revenue recognized associated with the bb2121 license and manufacturing services under our agreement with Celgene, of which \$13.9 million is attributable to differences resulting from the application of Topic 606 and ASC 605 to our arrangement with Celgene during the year ended December 31, 2018 and 2017, respectively, offset by a decrease in license and royalty revenue.

**Research and development expenses.** Research and development expenses were \$448.6 million for the year ended December 31, 2018, compared to \$273.0 million for the year ended December 31, 2017. The increase of \$175.5 million was primarily attributable to the following:

- \$84.5 million of increased costs incurred for material production, laboratory expenses, and collaboration research;
- \$61.1 million of increased employee compensation, benefit, and other headcount related expenses, of which \$27.8 million is stock based compensation expense, primarily due to an increase in headcount to support overall growth;
- \$17.8 million of increased facility related costs and professional and consulting fees;
- \$10.5 million of increased clinical trial-related costs to support the advancement of our clinical programs; and
- \$1.3 million of increased license and milestone fees (exclusive of any costs recorded in cost of license and royalty revenue) and increased grants and scholarships.

**General and administrative expenses.** General and administrative expenses were \$174.1 million for the year ended December 31, 2018, compared to \$93.6 million for the year ended December 31, 2017. The increase of \$80.6 million was primarily due to the following:

- \$47.4 million of increased employee compensation and benefits, inclusive of \$29.8 million of increased stock-based compensation expense;
- \$10.1 million of increased commercial-related costs, primarily attributed to market research costs;
- \$14.6 million due to increased consultant and professional services expenses;
- \$5.7 million in other headcount related costs; and
- \$4.3 million of increased office expenses.

These increases were offset by decreased facility-related costs of \$1.7 million.

**Cost of license and royalty revenue.** Cost of license and royalty revenue was \$0.9 million for the year ended December 31, 2018, compared to \$1.5 million for the year ended December 31, 2017. The decrease is attributable to decreased license and royalty revenue in the same periods.

**Change in fair value of contingent consideration.** The change in fair value of contingent consideration is driven by changes in assumptions related to estimate milestone achievement dates or probabilities of achievement.

**Interest income (expense), net.** The change in interest income (expense), net was primarily related to increased interest income earned on investments due to the increase in investment in marketable securities, partially offset by interest expense on the 60 Binney financing obligation.

**Other income (expense), net.** Other income, net was \$2.0 million for the year ended December 31, 2018, compared to other expense, net of \$1.3 million for the year ended December 31, 2017. The change is primarily related to an unrealized gain recognized on equity securities as well as fluctuations in foreign currency exchange rates.

**Comparison of the years ended December 31, 2017 and 2016:**

	<u>Year ended December 31,</u>		<u>Change</u>
	<u>2017</u>	<u>2016</u>	
	<u>(in thousands)</u>		
<b>Revenue:</b>			
Collaboration revenue	\$ 22,207	\$ 6,155	\$ 16,052
License and royalty revenue	13,220	-	13,220
Total revenues	35,427	6,155	29,272
<b>Operating expenses:</b>			
Research and development	273,040	204,775	68,265
General and administrative	93,550	65,119	28,431
Cost of license and royalty revenue	1,527	-	1,527
Change in fair value of contingent consideration	(525 )	4,091	(4,616 )
Total operating expenses	367,592	273,985	93,607
Loss from operations	(332,165 )	(267,830 )	64,335
Interest (expense) income, net	(2,001 )	3,782	5,783
Other expense, net	(1,267 )	(71 )	1,196
Loss before income taxes	(335,433 )	(264,119 )	71,314
Income tax (expense) benefit	(210 )	612	822
Net loss	\$ (335,643 )	\$ (263,507 )	\$ 72,136

**Revenue.** Total revenue was \$35.4 million for the year ended December 31, 2017, compared to \$6.2 million for the year ended December 31, 2016. The increase of \$29.3 million was primarily attributable to collaboration revenue recognized associated with the bb2121 license and manufacturing services which commenced in the first quarter of 2017 and revenue recognized under our out-licensing arrangements with Novartis and GSK.

**Research and development expenses.** Research and development expenses were \$273.0 million for the year ended December 31, 2017, compared to \$204.8 million for the year ended December 31, 2016. The increase of \$68.3 million was primarily attributable to the following:

- \$22.1 million of employee compensation and benefits, inclusive of \$6.9 million increased stock-based compensation expense, as well as \$2.2 million in other headcount related costs primarily due to an increase in headcount to support overall growth;
- \$17.7 million of manufacturing costs for our ongoing clinical and pre-clinical studies;
- \$12.1 million of clinical trial-related costs to support the advancement of our clinical programs;
- \$4.4 million of facility related costs;
- \$3.5 million of license and milestone fees; and
- \$3.0 million related to cost reimbursement to Celgene for costs incurred under our collaboration arrangement

**General and administrative expenses.** General and administrative expenses were \$93.6 million for the year ended December 31, 2017, compared to \$65.1 million for the year ended December 31, 2016. The increase of approximately \$28.4 million was primarily due to an increase of \$14.9 million in employee compensation and benefits, inclusive of \$6.6 million increased stock-based compensation expense, \$2.3 million in other headcount related costs, increased commercial-related costs of \$8.6 million primarily attributed to market research costs, and increased facility-related costs of \$2.1 million.

**Cost of license and royalty revenue.** Cost of license and royalty revenue was \$1.5 million for the year ended December 31, 2017. The increase compared to the prior period is attributable to increased license and royalty revenue in the same periods.

**Change in fair value of contingent consideration.** The change in fair value of contingent consideration is driven by changes in assumptions related to estimated milestone achievement dates or probabilities of achievement.

**Interest (expense) income, net.** The increase in interest (expense) income, net was primarily related to interest expense on the 60 Binney financing obligation partially offset by interest income earned on investments.

**Other expense, net.** Other expense, net was \$1.3 million for the year ended December 31, 2017, compared to \$0.1 million for the year ended December 31, 2016. The increase was primarily related to a loss on the disposal of assets.

#### Liquidity and Capital Resources

As of December 31, 2018, we had cash, cash equivalents and marketable securities of approximately \$1.9 billion. We expect cash, cash equivalents and marketable securities to fund planned operations into 2022. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2018, our funds are primarily held in U.S. Treasury securities, U.S. government agency securities, equity securities, certificates of deposit and money market accounts.

We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of December 31, 2018, we had an accumulated deficit of \$1.5 billion. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through public or private equity or debt financings, strategic collaborations, or other sources.

We have funded our operations principally from the sale of common stock in public offerings as outlined below, preferred stock and through the Celgene and Regeneron collaborations. Recent sources of equity financing include:

- In June 2017, we sold 4.4 million shares of common stock (inclusive of 0.6 million shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$105.00 per share for aggregate net proceeds to us of \$436.8 million.
- In December 2017, we sold 3.2 million shares of common stock (excluding any shares sold by us pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$185.00 per share for aggregate net proceeds to us of \$569.8 million.
- In January 2018, we sold 0.3 million shares of common stock pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the December 2017 underwritten public offering at a price of \$185.00 per share for aggregate net proceeds of \$48.7 million.
- In July 2018, we sold 3.9 million shares of common stock through an underwritten public offering at a price of \$162.50 per share for aggregate net proceeds to us of \$600.6 million.
- In August 2018, we sold 0.4 million shares of common stock to Regeneron in connection with our collaboration arrangement at a price of \$238.10 per share for aggregate net proceeds to us of \$100.0 million, of which \$45.5 million was attributed to a prepayment of joint research activities. See Note 10, “Collaborative Arrangements” in the Notes to Consolidated Financial Statements for more information.

### Sources of Liquidity

#### Cash Flows

The following table summarizes our cash flow activity:

	Year ended December 31,		
	2018	2017 (in thousands)	2016
Net cash used in operating activities	\$ (413,426)	\$ (280,553)	\$ (189,647)
Net cash (used in) provided by investing activities	(679,435)	(316,630)	67,110
Net cash provided by financing activities	737,692	1,076,174	241,534
Net (decrease) increase in cash, cash equivalents, and restricted cash	\$ (355,169)	\$ 478,991	\$ 118,997

*Operating Activities.* The net cash used in operating activities was \$413.4 million for the year ended December 31, 2018 and primarily consisted of a net loss of \$555.6 million adjusted for non-cash items including stock-based compensation of \$110.8 million, depreciation and amortization of \$17.2 million, offset by a net increase in operating assets and liabilities of \$19.2 million. The increase in operating assets and liabilities is driven by an increase in prepaid expenses and other assets of \$24.3 million primarily driven by upfront payments to contract manufacturing organizations and collaboration partners and a decrease in deferred revenue of \$41.9 million, offset by an increase of \$41.4 million in accounts payable, accrued expenses and other liabilities and an increase of \$44.0 million in collaboration research advancement.

The net cash used in operating activities was \$280.6 million for the year ended December 31, 2017 and primarily consisted of a net loss of \$335.6 million adjusted for non-cash items including stock-based compensation of \$53.3 million, depreciation and amortization of \$13.5 million, offset by a net increase in operating assets and liabilities of \$12.7 million. The increase in operating assets and liabilities is driven by an increase in prepaid expenses and other current assets of \$20.1 million primarily driven by upfront payments to contract manufacturing organizations offset by an increase of \$6.4 million in accounts payable, accrued expenses and other liabilities and an increase of \$1.0 million in deferred revenue.

The net cash used in operating activities was \$189.6 million for the year ended December 31, 2016 and primarily consisted of a net loss of \$263.5 million adjusted for non-cash items including stock-based compensation of \$39.8 million, depreciation and amortization of \$9.6 million, offset by a net increase in operating assets and liabilities of \$19.0 million. The increase in operating assets and liabilities is driven by an increase in prepaid expenses and other current assets of \$14.3 million for upfront payments to contract manufacturing organizations offset by an increase of \$28.7 million in accounts payable, accrued expenses and other liabilities related to an increase in manufacturing and clinical-trial related costs for our ongoing clinical and pre-clinical studies.

*Investing Activities.* Net cash used in investing activities for the year ended December 31, 2018 was \$679.4 million and was primarily due to the purchase of \$1,518.0 million of marketable securities and the purchase of \$55.7 million of property, plant and equipment offset by proceeds from the maturities of available-for-sale marketable securities of \$894.3 million.

Net cash used in investing activities for the year ended December 31, 2017 was \$316.6 million and was primarily due to the purchase of \$686.2 million of available-for-sale marketable securities and the purchase of \$62.2 million of property, plant and equipment offset by proceeds from the maturities of available-for-sale marketable securities of \$431.8 million.

Net cash provided by investing activities for the year ended December 31, 2016 was \$67.1 million and was primarily due to proceeds from the maturities of available-for-sale marketable securities of \$443.4 million offset by the purchase of \$348.2 million of available-for-sale marketable securities.

*Financing Activities:* Net cash provided by financing activities for the year ended December 31, 2018 was \$737.7 million and was primarily due to net cash proceeds from our January 2018 and July 2018 common stock offerings, as well as our issuance of common stock to Regeneron.

Net cash provided by financing activities for the year ended December 31, 2017 was \$1.1 billion and was primarily due to net cash proceeds from our June 2017 and December 2017 common stock offerings.

Net cash provided by financing activities for the year ended December 31, 2016 was \$241.5 million and was primarily due to net cash proceeds from our December 2016 common stock offering.

### ***Contractual Obligations and Commitments***

The following table summarizes our contractual obligations at December 31, 2018, which excludes potential milestone payments.

	<b>Total</b>	<b>2019</b>	<b>2020 through 2021</b> (in thousands)	<b>2022 through 2023</b>	<b>2024 and after</b>
60 Binney Street lease	\$ 166,798	\$ 18,974	\$ 38,949	\$ 40,324	\$ 68,551
Operating leases (1)	111,045	17,511	37,505	26,716	29,313
Contract manufacturing	233,856	69,827	88,886	49,351	25,792
Total contractual obligations	<u>\$ 511,699</u>	<u>\$ 106,312</u>	<u>\$ 165,340</u>	<u>\$ 116,391</u>	<u>\$ 123,656</u>

(1) Includes the lease of our lab and office space in Seattle, Washington, office space in Zug, Switzerland and rental payments associated with two embedded operating leases at contract manufacturing organizations.

We are subject to several in-licenses that include annual license maintenance fee payments and minimum royalties. The future obligations related to maintenance fee payments and minimum royalties in license agreements are not considered material and are not included in the table above.

#### ***60 Binney Street Lease***

On September 21, 2015, we entered into a lease agreement for office and laboratory space located at 60 Binney Street, Cambridge, Massachusetts. Under the terms of the lease, starting on October 1, 2016, we leased approximately 253,108 square feet at \$72.50 per square foot per year, or \$18.4 million per year in base rent, which is subject to scheduled annual rent increases of 1.75% plus certain operating expenses and taxes. We also executed a \$9.2 million letter of credit upon signing the lease, which was required to be collateralized with a bank account at a financial institution in accordance with the lease agreement. This letter of credit was increased to \$13.8 million during the third quarter of 2016 as required under the terms of the lease. Subject to the terms of the lease and certain reduction requirements specified therein, including market capitalization requirements, this amount may decrease back to \$9.2 million over time. The lease will continue until March 31, 2027. Pursuant to a work letter entered into in connection with the lease, the landlord will contribute an aggregate of \$42.4 million toward the cost of construction and tenant improvements for the building. The purpose of the lease was to replace our previously leased premises at 150 Second Street and 215 First Street in Cambridge, Massachusetts, both of which were fully exited during the first half of 2017. We occupied the building at 60 Binney Street beginning on March 27, 2017.

#### ***Operating Leases***

On June 3, 2016, we entered into a manufacturing agreement for the future commercial production of our Lenti-D and LentiGlobin product candidates with a contract manufacturing organization. Under this 12 year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, we were required to pay \$12.5 million upon the achievement of certain contractual milestones, and may pay up to \$8.0 million in additional contractual milestones if we elect our option to lease additional suites. We paid \$5.0 million for the achievement of the first and second contractual milestones during 2016 and paid \$5.5 million for the third and fourth contractual milestones achieved during 2017. In March 2018, \$1.5 million of the possible \$2.0 million related to the fifth contractual milestone was achieved and was paid in the second quarter of 2018. Given that construction was completed in March 2018, beginning in April 2018 we will pay \$5.1 million per year in fixed suite fees as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services, and may pay additional suite fees if it elects its option to reserve or lease additional suites. We may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. We concluded that this agreement contains an embedded lease as the suites are designated for our exclusive use during the term of the agreement. We concluded that we are not the deemed owner during construction nor is it a capital lease under ASC 840-10, Leases - Overall. As a result, we account for the agreement as an operating lease and expense the rental payments on a straight-line basis over the non-cancellable term of the embedded lease.

On November 18, 2016, we entered into an agreement for future clinical and commercial production of our LentiGlobin and Lenti-D gene therapy drug products with a contract manufacturing organization at an existing facility. The term of the agreement is five years with a three year renewal at the mutual option of each party. Under the agreement, we are required to pay an up-front fee of €3.0 million, €2.0 million of which was paid in the fourth quarter of 2016 and €1.0 million of which was paid in the third quarter of 2018, and annual maintenance and production fees of up to €9.8 million, depending on our production needs. We may terminate this agreement with twelve months' notice and a one-time termination fee. We concluded that this agreement contains an embedded lease as the clean rooms are designated for our exclusive use during the term of the agreement and determined that it is not a capital lease under ASC 840-10, Leases - Overall. As a result, we account for the agreement as an operating lease and expense the rental payments on a straight-line basis over the non-cancellable term of the embedded lease.

*Contingent Consideration Related to Business Combinations*

In connection with the Pregenex acquisition, we agreed to make contingent cash payments to the former equity holders of Pregenex. In accordance with accounting guidance for business combinations, these contingent cash payments are recorded as contingent consideration liabilities on our consolidated balance sheets at fair value. During the second quarter of 2017, a \$5.0 million preclinical milestone was achieved, which resulted in a \$5.0 million payment to the former equityholders of Pregenex during the third quarter of 2017. The aggregate remaining undiscounted amount of contingent consideration potentially payable is \$120.0 million. We have not included these payments in the table above because the achievement and timing of these milestones is not fixed and determinable. As of December 31, 2018, and 2017, \$5.2 million and \$2.2 million, respectively, is reflected as a non-current liability in the consolidated balance sheet, which represents the fair value of our contingent consideration obligations as of this date.

*Contingent Milestone and Royalty Payments*

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain development, regulatory and commercial milestones (such as the start of a clinical trial, filing of a BLA, approval by the FDA or product launch). We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not fixed and determinable.

Based on our development plans as of December 31, 2018, we may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with our collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. Because the achievement of these milestones or sales had not occurred as of December 31, 2018, such contingencies have not been recorded in our financial statements. Amounts related to contingent milestone payments and sales-based royalties are not yet considered contractual obligations as they are contingent upon success.

- Under a license agreement with Inserm-Transfert pursuant to which we license certain patents and know-how for use in adrenoleukodystrophy therapy, we will be required to make payments based upon development, regulatory and commercial milestones for any products covered by the in-licensed intellectual property. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €0.3, €0.2 and €1.6 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits. The royalty is subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.
- Under a license agreement with Institut Pasteur pursuant to which we license certain patents for use in *ex vivo* gene therapy, we will be required to make payments per product covered by the in-licensed intellectual property upon the achievement of development and regulatory milestones, depending on the indication and the method of treatment. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €1.5 and €2.0 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which varies slightly depending on the indication of the product. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the low single digits to mid-range double digits depending on the nature of the sublicense and stage of development. We are required to make an annual maintenance payment, which is creditable against royalty payments on a year-by-year basis. On April 1, 2015, we amended this license agreement with Institut Pasteur, which resulted in a payment of €3.0 million that was paid during the second quarter of 2015. During the year ended December 31, 2018 we paid Institut Pasteur €0.4 million in connection with amounts owed to us by sublicensees.
- Under a license agreement with the Board of Trustees of the Leland Stanford Junior University, or Stanford, pursuant to which we license the HEK293T cell line for use in gene therapy products, we are required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits that varies with net sales. The royalty is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.
- Under a license agreement with the Massachusetts Institute of Technology, or MIT, pursuant to which we license various patents, we will be required to make a payment of \$0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.

- Under a license agreement with Research Development Foundation pursuant to which we license patents that involve lentiviral vectors, we will be required to make payments of \$1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten years following first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends. During the year ended December 31, 2018 we paid Research Development Foundation \$0.1 million in connection with amounts owed to us by sublicensees.
- Under a license agreement with Biogen Inc., pursuant to which we license certain patents and patent applications related to our bb2121 and bb21217 product candidates, we will be required to make certain payments related to certain development milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$23.0 million in the aggregate for each licensed product upon the achievement of remaining milestones. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay a percentage of net sales as a royalty in the low single digits. During the year ended December 31, 2018 we paid Biogen \$5.0 million based upon a clinical development milestone for a product covered by the in-licensed intellectual property.
- Under a license agreement with the National Institutes of Health, or NIH, pursuant to which we license certain patent applications related to our bb2121 and bb21217 product candidates, we have agreed to certain development and regulatory milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$9.7 million in the aggregate for a licensed product upon the achievement of these milestones. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay NIH a percentage of net sales as a royalty in the low single digits. The royalties payable under this license agreement are subject to reduction for any third party payments required to be made, with a minimum floor in the low single digits.
- Under a license agreement with SIRION Biotech GmbH, or Sirion, pursuant to which we license certain patents directed to manufacturing related to our LentiGlobin product candidate, we will be required to make certain payments related to certain development milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$13.4 million in the aggregate for each product covered by the in-licensed intellectual property. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay Sirion a percentage of net sales as a royalty in the low single digits. The royalties payable under this license agreement are subject to reduction for any third party payments required to be made, with a minimum floor in the low single digits. During the year ended December 31, 2018 we paid Sirion \$1.4 million based upon a development milestone for a product covered by the in-licensed intellectual property.

#### *Other Funding Commitments*

We enter into contracts in the normal course of business with CROs for preclinical research studies and clinical trials, research supplies and other services and products for operating purposes. We have also entered into multi-year agreements with manufacturing partners in the United States and Europe (Brammer Bio, Novasep and SAFC Carlsbad, Inc., or SAFC, a subsidiary of MilliporeSigma), which are partnering with us on production of lentiviral vector across all of our programs. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. and apceth Biopharma, or apceth, to produce drug product for Lenti-D, LentiGlobin and bb21217. Currently, SAFC is the sole manufacturer of the lentiviral vector and apceth is the sole manufacturer of the drug product to support our potential commercial launch of LentiGlobin in Europe for the treatment of TDT. In our manufacturing agreement with SAFC, we are required to provide rolling forecasts for products on a quarterly basis, a portion of which will be considered a binding, firm order, subject to a purchase commitment. In our manufacturing agreement with apceth, we reserve production capacity for the manufacture of our drug product. Celgene manufactures drug product for bb2121. We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions and potential commercial launch. We are engaging in negotiations with apheresis centers that will be the centers for collection of HSCs from the patient and for infusion of drug product to the patient. For the treatment of patients with our drug product in the commercial setting, we intend to partner with participating apheresis centers, which we refer to as qualified treatment centers. In anticipation of the potential regulatory approval of LentiGlobin in Europe, we expect to first engage qualified treatment centers in Germany, Italy, and the United Kingdom in 2019. These contracts generally provide for termination on notice. Wherever contracts include stipulated commitment payments, we have included such payments in the table of contractual obligations and commitments.

#### **Off-Balance Sheet Arrangements**

As of December 31, 2018, we did not have any off-balance sheet arrangements as defined in the rules and regulations of the SEC.

**Item 7A. Quantitative and Qualitative Disclosures About Market Risks**

We are exposed to market risk related to changes in interest rates. As of December 31, 2018 and 2017, we had cash, cash equivalents and marketable securities of \$1.9 billion and \$1.6 billion, respectively, primarily invested in U.S. treasury securities, U.S. government agency securities, equity securities, federally insured certificates of deposit and money market accounts. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points, or one percentage point, from levels at December 31, 2018, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of \$9.6 million.

**Item 8. Financial Statements and Supplementary Data**

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

**Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure**

None.

**Item 9A. Controls and Procedures**

*Evaluation of Disclosure Controls and Procedures*

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a- 15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")), as of the end of the period covered by this Annual Report on Form 10-K. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective.

*Management's Annual Report on Internal Control Over Financial Reporting*

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements. Under the supervision and with the participation of management, including our principal executive and financial officers, we assessed our internal control over financial reporting as of December 31, 2018, based on criteria for effective internal control over financial reporting established in Internal Control - Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2018, based on criteria established in the COSO 2013 framework.

The effectiveness of our internal control over financial reporting as of December 31, 2018 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

***Inherent Limitations of Internal Controls***

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within our company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

***Changes in Internal Control over Financial Reporting***

We utilize a third-party cloud-based ERP system in our financial reporting. In the fourth quarter of 2018, the ERP service provider made changes to its internal controls to address deficiencies related to its information technology change management controls.

**Report of Independent Registered Public Accounting Firm**

To the Stockholders and the Board of Directors of bluebird bio, Inc.

**Opinion on Internal Control over Financial Reporting**

We have audited bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, bluebird bio, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2018, and the related notes and our report dated February 21, 2019 expressed an unqualified opinion thereon.

**Basis for Opinion**

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

**Definition and Limitations of Internal Control Over Financial Reporting**

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP  
Boston, Massachusetts  
February 21, 2019

**Item 9B. Other Information**

Our policy governing transactions in our securities by our directors, officers, and employees permits our officers, directors and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended. We have been advised that certain of our officers (including David Davidson (Chief Medical Officer), Philip Gregory (Chief Scientific Officer), Jason Cole (Chief Operating and Legal Officer), Jeffrey Walsh (Chief Strategy Officer), Kory Wentworth (Vice President, Finance and Treasurer), and certain of our directors (including James Mandell) have entered into trading plans covering periods after the date of this annual report on Form 10-K in accordance with Rule 10b5-1 and our policy governing transactions in our securities. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company. We do not undertake to report Rule 10b5-1 trading plans that may be adopted by any officers or directors in the future, or to report any modifications or termination of any publicly announced trading plan, except to the extent required by law.

**PART III**

**Item 10. Directors, Executive Officers and Corporate Governance**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 11. Executive Compensation**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 13. Certain Relationships and Related Transactions and Director Independence**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 14. Principal Accountant Fees and Services**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**PART IV**

**Item 15. Exhibits and Financial Statement Schedules**

(a)(1) Financial Statements.

The response to this portion of Item 15 is set forth under Item 8 above.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Consolidated Financial Statements or Notes thereto set forth under Item 8 above.

(a)(3) Exhibits.

See the Exhibit Index immediately before the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are filed or incorporated by reference as part of this Annual Report on Form 10-K.

**Item 16. Form 10-K Summary**

Not applicable.

**bluebird bio, Inc.**

**Index to Consolidated Financial Statements**

	<u>Pages</u>
<a href="#"><u>Report of Independent Registered Public Accounting Firm</u></a>	F-2
<a href="#"><u>Consolidated Balance Sheets</u></a>	F-3
<a href="#"><u>Consolidated Statements of Operations and Comprehensive Loss</u></a>	F-4
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**Report of Independent Registered Public Accounting Firm**

To the Stockholders and the Board of Directors of bluebird bio, Inc.

**Opinion on the Financial Statements**

We have audited the accompanying consolidated balance sheets of bluebird bio, Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 21, 2019 expressed an unqualified opinion thereon.

**Adoption of New Accounting Standard**

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), and the related amendments.

**Basis for Opinion**

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2012.

Boston, Massachusetts

February 21, 2019

**bluebird bio, Inc.****Consolidated Balance Sheets  
(in thousands, except per share amounts)**

	<u>As of December 31,</u>	
	<u>2018</u>	<u>2017</u>
<b>Assets</b>		
Current Assets:		
Cash and cash equivalents	\$ 402,579	\$ 758,505
Marketable securities	982,725	531,604
Tenant improvement receivable	19	3,112
Prepaid expenses	19,762	21,171
Receivables and other current assets	13,912	8,377
Total current assets	<u>1,418,997</u>	<u>1,322,769</u>
Marketable securities	506,123	324,193
Property, plant and equipment, net	246,622	199,606
Intangible assets, net	13,169	16,931
Goodwill	13,128	13,128
Restricted cash and other non-current assets	44,805	23,940
Total assets	<u>\$ 2,242,844</u>	<u>\$ 1,900,567</u>
<b>Liabilities and Stockholders' Equity</b>		
Current Liabilities:		
Accounts payable	\$ 17,831	\$ 12,873
Accrued expenses and other current liabilities	99,393	57,065
Deferred revenue, current portion	18,602	25,674
Collaboration research advancement, current portion	10,605	-
Total current liabilities	<u>146,431</u>	<u>95,612</u>
Deferred revenue, net of current portion	16,338	21,763
Collaboration research advancement, net of current portion	33,349	-
Contingent consideration	5,230	2,231
Financing lease obligation, net of current portion	153,319	154,749
Other non-current liabilities	3,107	2,780
Total liabilities	<u>357,774</u>	<u>277,135</u>
Commitments and contingencies (Note 8)		
Stockholders' Equity:		
Preferred stock, \$0.01 par value, 5,000 shares authorized; 0 shares issued and outstanding at December 31, 2018 and December 31, 2017	-	-
Common stock, \$0.01 par value, 125,000 shares authorized; 54,738 and 49,406 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	547	494
Additional paid-in capital	3,386,958	2,540,951
Accumulated other comprehensive loss	(3,627 )	(4,205 )
Accumulated deficit	(1,498,808 )	(913,808 )
Total stockholders' equity	<u>1,885,070</u>	<u>1,623,432</u>
Total liabilities and stockholders' equity	<u>\$ 2,242,844</u>	<u>\$ 1,900,567</u>

*See accompanying notes to consolidated financial statements.*

**bluebird bio, Inc.****Consolidated Statements of Operations and Comprehensive Loss**  
(in thousands, except per share amounts)

	<b>Year ended December 31,</b>		
	<b>2018</b>	<b>2017</b>	<b>2016</b>
<b>Revenue:</b>			
Collaboration revenue	\$ 52,353	\$ 22,207	\$ 6,155
License and royalty revenue	2,226	13,220	-
Total revenues	<u>54,579</u>	<u>35,427</u>	<u>6,155</u>
<b>Operating expenses:</b>			
Research and development	448,589	273,040	204,775
General and administrative	174,129	93,550	65,119
Cost of license and royalty revenue	885	1,527	-
Change in fair value of contingent consideration	2,999	(525 )	4,091
Total operating expenses	<u>626,602</u>	<u>367,592</u>	<u>273,985</u>
Loss from operations	(572,023 )	(332,165 )	(267,830 )
Interest income (expense), net	14,624	(2,001 )	3,782
Other income (expense), net	1,961	(1,267 )	(71 )
Loss before income taxes	<u>(555,438 )</u>	<u>(335,433 )</u>	<u>(264,119 )</u>
Income tax (expense) benefit	(187 )	(210 )	612
Net loss	<u>\$ (555,625 )</u>	<u>\$ (335,643 )</u>	<u>\$ (263,507 )</u>
Net loss per share - basic and diluted	<u>\$ (10.68 )</u>	<u>\$ (7.71 )</u>	<u>\$ (7.07 )</u>
Weighted-average number of common shares used in computing net loss per share - basic and diluted	<u>52,032</u>	<u>43,535</u>	<u>37,284</u>
<b>Other comprehensive income (loss):</b>			
Other comprehensive income (loss), net of tax expense of \$0.4, \$0.0 and \$0.6 million for the years ended December 31, 2018, 2017 and 2016, respectively	578	(3,056 )	1,142
Total other comprehensive income (loss)	<u>578</u>	<u>(3,056 )</u>	<u>1,142</u>
Comprehensive loss	<u>\$ (555,047 )</u>	<u>\$ (338,699 )</u>	<u>\$ (262,365 )</u>

*See accompanying notes to consolidated financial statements.*

## bluebird bio, Inc.

Consolidated Statements of Stockholders' Equity  
(in thousands)

	<u>Common stock</u>		<u>Additional paid-in capital</u>	<u>Accumulated other comprehensive loss</u>	<u>Accumulated deficit</u>	<u>Total stockholders' equity</u>
	<u>Shares</u>	<u>Amount</u>				
<b>Balances at December 31, 2015</b>	36,894	\$ 369	\$ 1,166,585	\$ (2,291 )	\$ (314,167 )	\$ 850,496
Vesting of restricted stock units	113	1	(1 )	-	-	-
Issuance of common stock upon public offering, net of issuance costs of \$15,269	3,289	33	234,698	-	-	234,731
Exercise of stock options	377	4	6,141	-	-	6,145
Purchase of common stock under ESPP	18	-	677	-	-	677
Stock-based compensation	-	-	39,756	-	-	39,756
Unrealized gain on available-for-sale securities, net of tax	-	-	-	1,142	-	1,142
Net loss	-	-	-	-	(263,507 )	(263,507 )
<b>Balances at December 31, 2016</b>	40,691	\$ 407	\$ 1,447,856	\$ (1,149 )	\$ (577,674 )	\$ 869,440
Retroactive adjustment to beginning accumulated deficit and additional paid-in capital resulting from adoption of ASU 2016-09	-	-	491	-	(491 )	-
Vesting of restricted stock units	88	1	(1 )	-	-	-
Issuance of common stock upon public offering, net of issuance costs of \$53,487	7,625	76	1,006,494	-	-	1,006,570
Exercise of stock options	981	10	31,676	-	-	31,686
Purchase of common stock under ESPP	21	-	1,153	-	-	1,153
Stock-based compensation	-	-	53,282	-	-	53,282
Other comprehensive loss	-	-	-	(3,056 )	-	(3,056 )
Net loss	-	-	-	-	(335,643 )	(335,643 )
<b>Balances at December 31, 2017</b>	49,406	\$ 494	\$ 2,540,951	\$ (4,205 )	\$ (913,808 )	\$ 1,623,432
Adjustment to beginning accumulated deficit from adoption of ASU 2014-09	-	-	-	-	(29,375 )	(29,375 )
Vesting of restricted stock units	152	2	(2 )	-	-	-
Issuance of common stock upon public offering, net of issuance costs of \$34,588	4,169	42	649,326	-	-	649,368
Issuance of common stock to Regeneron	420	4	54,480	-	-	54,484
Exercise of stock options	575	5	29,763	-	-	29,768
Purchase of common stock under ESPP	16	-	1,604	-	-	1,604
Stock-based compensation	-	-	110,836	-	-	110,836
Other comprehensive loss	-	-	-	578	-	578
Net loss	-	-	-	-	(555,625 )	(555,625 )
<b>Balances at December 31, 2018</b>	54,738	\$ 547	\$ 3,386,958	\$ (3,627 )	\$ (1,498,808 )	\$ 1,885,070

See accompanying notes to consolidated financial statements.

**bluebird bio, Inc.****Consolidated Statements of Cash Flows  
(in thousands)**

	<b>Year ended December 31,</b>		
	<b>2018</b>	<b>2017</b>	<b>2016</b>
<b>Cash flows from operating activities:</b>			
Net loss	\$ (555,625 )	\$ (335,643 )	\$ (263,507 )
Adjustments to reconcile net loss to net cash used in operating activities:			
Change in fair value of contingent consideration	2,999	(2,189 )	2,675
Depreciation and amortization	17,158	13,538	9,648
Stock-based compensation expense	110,836	53,282	39,756
Unrealized gain on equity securities	(2,154 )	-	-
Other non-cash items	(5,880 )	3,153	2,825
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(24,288 )	(20,092 )	(14,318 )
Accounts payable	3,614	526	6,658
Accrued expenses and other liabilities	37,832	5,848	22,051
Deferred revenue	(41,872 )	1,024	4,565
Collaboration research advancement	43,954	-	-
Net cash used in operating activities	<u>(413,426 )</u>	<u>(280,553 )</u>	<u>(189,647 )</u>
<b>Cash flows from investing activities:</b>			
Purchase of property, plant and equipment, including assets under financing lease obligation	(55,737 )	(62,242 )	(28,029 )
Purchases of marketable securities	(1,517,982 )	(686,204 )	(348,225 )
Proceeds from maturities of marketable securities	894,284	431,816	443,364
Net cash (used in) provided by investing activities	<u>(679,435 )</u>	<u>(316,630 )</u>	<u>67,110</u>
<b>Cash flows from financing activities:</b>			
Cash paid for contingent purchase price consideration	-	(1,074 )	(2,025 )
Reimbursement of assets under financing lease obligation	3,098	38,021	1,663
Payments on financing lease obligation	(1,017 )	(574 )	-
Proceeds from public offering of common stock, net of issuance costs	649,368	1,006,570	234,962
Proceeds from exercise of stock options and ESPP contributions	31,759	33,231	6,934
Proceeds from issuance of common stock to Regeneron	54,484	-	-
Net cash provided by financing activities	<u>737,692</u>	<u>1,076,174</u>	<u>241,534</u>
(Decrease) increase in cash, cash equivalents and restricted cash	(355,169 )	478,991	118,997
Cash, cash equivalents and restricted cash at beginning of year	772,268	293,277	174,280
Cash, cash equivalents and restricted cash at end of year	<u>\$ 417,099</u>	<u>\$ 772,268</u>	<u>\$ 293,277</u>
<b>Supplemental cash flow disclosures:</b>			
Cash paid for interest in connection with financing lease obligation	\$ 15,494	\$ 11,411	\$ -
<b>Supplemental cash flow disclosures from investing and financing activities:</b>			
Assets acquired under financing lease obligation	\$ -	\$ 3,271	\$ 48,034
Purchases of property, plant and equipment included in accounts payable and accrued expenses	\$ 7,449	\$ 2,566	\$ 6,363
Tenant improvements under financing lease included in tenant improvements receivable	\$ 14	\$ 3,112	\$ 8,542

*See accompanying notes to consolidated financial statements.*

**bluebird bio, Inc.****Notes to Consolidated Financial Statements  
For the Years Ended December 31, 2018, 2017 and 2016****1. Description of the business**

bluebird bio, Inc. (the “Company” or “bluebird”) was incorporated in Delaware on April 16, 1992, and is headquartered in Cambridge, Massachusetts. The Company researches, develops, manufactures and plans to commercialize gene therapies for severe genetic diseases and cancer. Since its inception, the Company has devoted substantially all of its resources to its research and development efforts relating to its product candidates, including activities to manufacture product candidates, conduct clinical studies of its product candidates, perform preclinical research to identify new product candidates and provide general and administrative support for these operations.

The Company’s clinical programs in severe genetic diseases include its LentiGlobin® product candidate to treat transfusion-dependent β-thalassemia, or TDT, and to treat sickle cell disease, or SCD, and its Lenti-DTM product candidate to treat cerebral adrenoleukodystrophy, or CALD, a rare hereditary neurological disorder. In the second half of 2018, the Company filed a marketing authorization application with the EMA for the LentiGlobin product candidate for the treatment of adult and adolescent patients with TDT and non-  $\beta^0/\beta^0$  genotypes. If the application is approved, the Company expects to begin commercializing and generating product revenues in the second half of 2019. The Company’s programs in oncology are focused on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. bb2121 and bb21217, which are product candidates in oncology under the Company’s collaboration arrangement with Celgene Corporation (“Celgene”), are CAR T cell product candidates for the treatment of multiple myeloma. Refer to Note 10, “*Collaborative arrangements*” for further discussion of the Company’s collaboration with Celgene.

As of December 31, 2018, the Company had cash, cash equivalents and marketable securities of \$1.9 billion. Although the Company has incurred recurring losses and expects to continue to incur losses for the foreseeable future, the Company expects its cash, cash equivalents and marketable securities will be sufficient to fund current planned operations for at least the next twelve months.

**2. Summary of significant accounting policies and basis of presentation*****Basis of presentation***

The accompanying consolidated financial statements have been prepared by the Company in accordance with accounting principles generally accepted in the United States (“GAAP”) as found in the Accounting Standards Codification (“ASC”) and Accounting Standards Updates (“ASUs”) of the Financial Accounting Standards Board (“FASB”). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States GAAP as found in the ASC and ASUs of the FASB.

Certain items in the prior year’s consolidated financial statements have been reclassified to conform to the current presentation. As a result, no subtotals in the prior year consolidated financial statements were impacted.

Amounts reported are computed based on thousands, except percentages, per share amounts, and as otherwise noted. As a result, certain totals may not sum due to rounding.

***Principles of consolidation***

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

The Company continually assesses whether it is the primary beneficiary of a variable interest entity as changes to existing relationships or future transactions may result in consolidation or deconsolidation of one or more collaborators or partners. In determining whether it is the primary beneficiary of an entity in which the Company has a variable interest, management applies a qualitative approach that determines whether the Company has both (1) the power to direct the economically significant activities of the entity and (2) the obligation to absorb losses of, or the right to receive benefits from, the entity that could potentially be significant to that entity.

#### ***Use of estimates***

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements.

Estimates and judgments are used in the following areas, among others: fair value estimates used to assess potential impairment of long-lived assets, including goodwill and intangible assets, financing lease obligations, contingent consideration, stock-based compensation expense, accrued expenses, and income taxes. In addition, estimates and judgments are used in the Company's accounting for its revenue-generating arrangements, in particular as it relates to determining the standalone selling price of performance obligations, evaluating whether an option to acquire additional goods and services represents a material right, estimating the total transaction price, including estimating variable consideration and the probability of achieving future potential development and regulatory milestones, and the period of performance over which revenue may be recognized.

#### ***Foreign currency translation***

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for stockholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in stockholders' equity. Foreign currency transaction gains and losses are included in other expense, net in the results of operations.

#### ***Segment information***

The Company operates in a single segment, focusing on the development of potentially transformative gene therapies for severe genetic diseases and cancer. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting. All material long-lived assets of the Company reside in the United States.

#### ***Cash and cash equivalents***

The Company considers all highly liquid investments purchased with original final maturities of 90 days or less from the date of purchase to be cash equivalents. Cash and cash equivalents comprise marketable securities with maturities of less than 90 days when purchased. Cash equivalents are reported at fair value.

#### ***Marketable securities***

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current. The Company's marketable securities are maintained by investment managers and consist of U.S. Treasury securities, U.S. government agency securities, equity securities, certificates of deposit, and money market accounts. Debt securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the instrument. Equity securities with readily determinable fair values are also carried at fair value with unrealized gains and losses included in other income (expense), net. Realized gains and losses on both debt and equity securities are determined using the specific identification method and are included in other income (expense), net.

The Company classifies equity securities with readily determinable fair values, which would be available for use in its current operations, as current assets even though the Company may not dispose of such marketable securities within the next 12 months.

If any adjustment to fair value reflects a decline in value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, marks the investment to market through a charge to the Company's statement of operations and comprehensive loss.

#### ***Concentrations of credit risk and off-balance sheet risk***

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and available-for-sale securities. The Company maintains its cash and cash equivalent balances with high-quality financial institutions and, consequently, the Company believes that such funds are subject to minimal credit risk. The Company's marketable securities primarily consist of U.S. Treasury securities, U.S. government agency securities and certificates of deposit, and potentially subject the Company to concentrations of credit risk. The Company has adopted an investment policy that limits the amounts the Company may invest in any one type of investment and requires all investments held by the Company to be at least AA+/Aa1 rated, thereby reducing credit risk exposure.

#### ***Fair value of financial instruments***

The Company has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements

Level 1-Fair values are determined utilizing quoted prices (unadjusted) in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2-Fair values are determined utilizing quoted prices for identical or similar assets or liabilities in active markets or other market observable inputs such as interest rates, yield curves and foreign currency spot rates.

Level 3-Prices or valuations that require inputs that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include marketable securities (see Note 3, "Marketable securities" and Note 4, "Fair value measurements") and contingent consideration (see Note 4, "Fair value measurements"). The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term nature.

#### ***Business combinations***

Business combinations are accounted for using the acquisition method of accounting. Using this method, the tangible and intangible assets acquired and the liabilities assumed are recorded as of the acquisition date at their respective fair values. The Company evaluates a business as an integrated set of activities and assets that is capable of being managed for the purpose of providing a return in the form of dividends, lower costs or other economic benefits and consists of inputs and processes that provide or have the ability to provide outputs. In an acquisition of a business, the excess of the fair value of the consideration transferred over the fair value of the net assets acquired is recorded as goodwill. In an acquisition of net assets that does not constitute a business, no goodwill is recognized.

The consolidated financial statements include the results of operations of an acquired business after the completion of the acquisition. See Note 4, "Fair value measurements," for additional information.

#### ***Goodwill***

Goodwill represents the excess of the purchase price over the fair value of the net assets acquired when accounted for using the acquisition method of accounting for business combinations. Goodwill is not amortized but is evaluated for impairment within the Company's single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the Company's reporting unit below its carrying amount. The Company has not recognized any impairment charges related to goodwill to date.

#### ***Intangible assets***

Intangible assets consist of acquired core technology with finite lives. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives and periodically reviews for impairment.

#### ***Contingent consideration***

Each reporting period, the Company revalues the contingent consideration obligations associated with business combinations to their fair value and records within operating expenses increases in their fair value as contingent consideration expense and decreases in the fair value as contingent consideration income. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones may be achieved, and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as development of the Company's programs in certain indications progress and additional data are obtained, impacting the Company's assumptions. The assumptions used in estimating fair value require significant judgment. The use of different assumptions and judgments could result in a materially different estimate of fair value. See Note 4, "*Fair value measurements*," for additional information.

#### ***Property, plant and equipment***

Property, plant and equipment is stated at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Depreciation and amortization is calculated using the straight-line method over the estimated useful lives of the assets, which are as follows:

Asset	Estimated useful life
Building	40 years
Computer equipment and software	3 years
Furniture and fixtures	2-5 years
Laboratory equipment	2-5 years
Leasehold improvements	Shorter of the useful life or remaining lease term

The Company records certain costs incurred and reported by a landlord as an asset and corresponding financing lease obligation on the consolidated balance sheets. See Note 8, "*Commitments and contingencies*," for additional information.

#### ***Impairment of long-lived assets***

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets.

#### ***Financing lease obligation***

Beginning in 2015 and through construction completion in 2017, the Company recorded certain estimated construction costs incurred and reported to the Company by the landlord for its 60 Binney Street location as an asset and corresponding financing lease obligation on the consolidated balance sheets because it was deemed to be the owner of the building during the construction period for accounting purposes. Any costs incurred by the Company that have been reimbursed by the landlord or that qualify for reimbursement by the landlord are recorded as an asset and financing lease obligation. Any incremental costs incurred directly by the Company that do not qualify for reimbursement by the landlord are also capitalized. Upon completion of the construction of the building in the first quarter of 2017, the Company evaluated the lease and determined that it did not meet the criteria for "sale-leaseback" treatment. Accordingly, the Company is depreciating the building over 40 years and incurring interest expense in its consolidated statement of operations and comprehensive loss related to the financing lease obligation recorded on its consolidated balance sheet. The Company bifurcates its lease payments pursuant to the lease into (i) a portion that is allocated to the financing obligation related to the building and (ii) a portion that is allocated to the land on which the building was constructed. The portion of the lease obligation allocated to the land is treated for accounting purposes as an operating lease that commenced in September 2015 and is recorded on a straight-line basis over the initial lease term. See Note 8, "*Commitments and contingencies*," for additional information.

### ***Revenue recognition***

Effective January 1, 2018, the Company adopted Accounting Standards Codification (“ASC”), Topic 606, *Revenue from Contracts with Customers* (“Topic 606”), using the modified retrospective transition method. Under this method, the Company has recognized the cumulative effect of the adoption as an adjustment to the opening balance of accumulated deficit in the current period consolidated balance sheet. The Company has not revised its consolidated financial statements for prior periods. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer’s discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations. The identification of material rights requires judgments related to the determination of the value of the underlying license relative to the option exercise price, including assumptions about technical feasibility and the probability of developing a candidate that would be subject to the option rights. The exercise of a material right is accounted for as a contract modification for accounting purposes.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity’s promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices (“SSP”) on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. The Company assessed each of its revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of its arrangements.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

#### *Collaboration revenue*

To date, the Company's collaboration revenue has been generated from its collaboration arrangements with Celgene and Regeneron Pharmaceuticals, Inc. ("Regeneron"), as further described in Note 10, "*Collaborative arrangements*".

The Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808") to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. Amounts that are owed to collaboration partners are recognized as an offset to collaboration revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed the Company's collaboration revenues in each quarterly period, such amounts are classified as research and development expense. For those elements of the arrangement that are accounted for pursuant to Topic 606, the Company applies the five-step model described above.

#### *License and royalty revenue*

The Company enters into out-licensing agreements that are within the scope of Topic 606. The Company does not have any material license arrangements that contain more than one performance obligation. The terms of such out-license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of the licensor's ongoing activities, and typically include payment of one or more of the following: non-refundable up-front license fees; development and regulatory milestone payments and milestone payments based on the level of sales; and royalties on net sales of licensed products. Nonrefundable up-front license fees are recognized as revenue at a point in time when the licensed intellectual property is made available for the customer's use and benefit, which is generally at the inception of the arrangement. Development and regulatory milestone fees, which are a type of variable consideration, are recognized as revenue to the extent that it is probable that a significant reversal will not occur. The Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

For a complete discussion of accounting for collaboration and other revenue-generating arrangements, see Note 10, "*Collaborative arrangements*" and Note 11, "*License and royalty revenue*". Additionally, see "*Recent accounting pronouncements - Recently adopted*" below for discussion of the impact of adopting Topic 606, which was effective on January 1, 2018.

#### ***Research and development expenses***

Research and development costs are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, license and milestone fees, contract services and other related costs. Research and development costs, including up-front fees and milestones paid to collaborators, are also expensed as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense. The Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants, or other clinical trial vendors that perform the activities. The Company recognizes the reimbursement associated with collaborative activities to its collaborative partners as research and development expense in the period the services are provided.

#### ***Cost of license and royalty revenue***

Cost of license and royalty revenue represents expense associated with amounts owed to third parties as a result of revenue recognized under the Company's out-license arrangements.

#### ***Stock-based compensation***

The Company's share-based compensation programs grant awards that have included stock options, restricted stock units, restricted stock awards, and shares issued under its employee stock purchase plan. Grants are awarded to employees, and non-employees, including directors.

The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation-Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

The Company's stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees, directors, and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company expenses restricted stock unit awards to employees and non-employees based on the fair value of the award on a straight-line basis over the associated service period of the award.

The Company estimates the fair value of its option awards to employees, directors, and non-employees using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of complete company-specific historical and implied volatility data for the full expected term of the stock-based awards, the Company bases its estimate of expected volatility on a representative group of publicly traded companies in addition to its own volatility data. For these analyses, the Company selected companies with comparable characteristics to its own, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The Company has estimated the expected term of its employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future.

As a result of the adoption of ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, effective January 1, 2017, the Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Prior to the adoption of Accounting Standards Update (“ASU”) No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award.

#### ***Interest income (expense), net***

Interest income (expense), net consists primarily of interest income earned on investments, net of amortization of premium and accretion of discount which is partially offset by interest expense on the Company’s 60 Binney Street financing lease obligation. Interest income was approximately \$30.1 million, \$9.5 million, and \$3.8 million for the years ended December 31, 2018, 2017, and 2016, respectively. Interest expense was \$15.5 million, \$11.4 million, and \$0 for the years ended December 31, 2018, 2017, and 2016, respectively. Please refer to Note 8, “*Commitments and contingencies*,” for further discussion of interest expense incurred on the 60 Binney Street lease.

#### ***Other income (expense), net***

Other income (expense), net consists primarily of unrealized gains on equity securities, gains and losses on the disposal of fixed assets, realized gains and losses on debt securities, and gains and losses on foreign currency transactions.

#### ***Net loss per share***

Basic net loss per share is calculated by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period. Diluted net income per share is calculated by dividing the net income attributable to common stockholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options, unvested restricted stock, restricted stock units, and employee stock purchase plan stock using the treasury stock method. Given that the Company recorded a net loss for each of the periods presented, there is no difference between basic and diluted net loss per share since the effect of common stock equivalents would be anti-dilutive and are, therefore, excluded from the diluted net loss per share calculation.

The Company follows the two-class method when computing net loss per share in periods when issued shares that meet the definition of participating securities are outstanding. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to received dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders when participating securities are outstanding, losses are not allocated to the participating securities.

#### ***Income taxes***

Income taxes are recorded in accordance with FASB ASC Topic 740, Income Taxes (“ASC 740”), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. The Company accrues for potential interest and penalties related to unrecognized tax benefits in income tax expense.

#### ***Comprehensive loss***

Comprehensive loss is composed of net loss and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on debt securities, foreign currency translation adjustments and other items.

***Recent accounting pronouncements*****Recently adopted*****ASU No. 2014-09, Revenue from Contracts with Customers***

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers*, which superseded the revenue recognition requirements in ASC 605, *Revenue Recognition* and created a new Topic 606, *Revenue from Contracts with Customers*. In 2015 and 2016, the FASB issued additional ASUs related to Topic 606 that delayed the effective date of the guidance and clarified various aspects of the new revenue guidance. The new standard became effective on January 1, 2018. Topic 606 allows for either a full retrospective adoption, in which the standard is applied to all periods presented in an entity's financial statements, or a modified retrospective approach, in which the standard is applied to the most current period presented in an entity's financial statements with the cumulative effect of adoption recognized as an adjustment to the opening balance of accumulated deficit in the period of adoption. The Company adopted this new standard on January 1, 2018 using the modified retrospective approach, which has been applied consistently to all contracts, and has elected to use the following practical expedient that is permitted under the rules of adoption:

- For contracts that were modified prior to Topic 606 adoption, the Company has not retrospectively accounted for each contract modification in accordance with the contract modification guidance. Instead, the Company reflected the aggregate effect of all modifications occurring prior to Topic 606 adoption when identifying the satisfied and unsatisfied performance obligations, determining the transaction price and allocating the transaction price.

As a result of adopting Topic 606, the Company recorded a \$29.4 million adjustment to the opening balance of accumulated deficit in the first quarter of 2018 primarily as a result of the accounting for the up-front consideration received in March 2013 in connection with the collaboration arrangement with Celgene under ASC 605-25 versus Topic 606. Refer below for a summary of the amount by which each financial statement line item was affected by the impact of the cumulative adjustment:

**Impact of Topic 606 adoption on  
consolidated balance sheet  
as of January 1, 2018**

(in thousands)	As reported under Topic 606	Adjustments	Balances without adoption of Topic 606
Deferred revenue, current portion	\$ 45,344	\$ 19,670	\$ 25,674
Deferred revenue, net of current portion	\$ 31,468	\$ 9,705	\$ 21,763
Accumulated deficit	\$ (943,183 )	\$ (29,375 )	\$ (913,808 )

The amount by which each financial statement line item is affected in the current reporting period by Topic 606 as compared with the guidance that was in effect prior to adoption is disclosed below.

**Impact of Topic 606 adoption on  
consolidated balance sheet  
as of December 31, 2018**

(in thousands)	As reported under Topic 606	Adjustments	Balances without adoption of Topic 606
Deferred revenue, current portion	\$ 18,602	\$ 7,772	\$ 10,830
Deferred revenue, net of current portion	\$ 16,338	\$ 3,094	\$ 13,244
Accumulated deficit	\$ (1,498,808 )	\$ (10,866 )	\$ (1,487,942 )

**Impact of Topic 606 adoption on consolidated  
statement of operations and comprehensive loss  
for the twelve months ended December 31, 2018**

(in thousands, except per share data)	As reported under Topic 606	Adjustments	Balances without adoption of Topic 606
Collaboration revenue	\$ 52,353	\$ 13,917	\$ 38,436
Research and development expense	\$ 448,589	\$ (4,592 )	\$ 453,181
Net loss	\$ (555,625 )	\$ 18,509	\$ (574,134 )
Net loss per share - basic and diluted:	\$ (10.68 )	\$ 0.35	\$ (11.03 )

**Impact of Topic 606 adoption on  
consolidated statement of cash flows  
for the twelve months ended December 31, 2018**

(in thousands)	As reported under Topic 606	Adjustments	Balances without adoption of Topic 606
Net loss	\$ (555,625)	\$ 18,509	\$ (574,134)
Changes in deferred revenue	\$ (41,872)	\$ (18,509)	\$ (23,363)

The most significant change above relates to the Company's collaboration revenue, which to date has been primarily generated from its collaboration arrangement with Celgene. Under ASC 605, the Company accounted for contract modifications to the Celgene collaboration as they occurred and the accounting for those changes was prospective in nature. Through the application of the practical expedient discussed above in connection with the adoption of Topic 606, the Company reflected the aggregate effect of all modifications to the Celgene collaboration when identifying the satisfied and unsatisfied performance obligations, determining the transaction price, and allocating the transaction price. As a result, although the performance obligations identified under Topic 606 were generally consistent with the units of account identified under ASC 605, the timing of the allocation of the transaction price to the identified performance obligations under Topic 606 differed from the allocations of consideration under ASC 605. Accordingly, the transaction price ultimately allocated to each performance obligation under Topic 606 differed from the amounts allocated under ASC 605.

As a result of adopting Topic 606, the Company established a deferred revenue deferred tax asset, and an offsetting valuation allowance, of \$7.9 million through its accumulated deficit given it is not more likely than not that the deferred tax asset will be realized due to historical and expected future losses, such that there was no tax impact on the Company's consolidated financial statements as a result of adopting Topic 606.

*ASU 2016-15, Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments*

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments* ("Topic 230"). The new standard clarifies certain aspects of the statement of cash flows, including the classification of contingent consideration payments made after a business combination and several other clarifications not currently applicable to the Company. The new standard also clarifies that an entity should determine each separately identifiable source or use within the cash receipts and cash payments on the basis of the nature of the underlying cash flows. In situations in which cash receipts and payments have aspects of more than one class of cash flows and cannot be separated by source or use, the appropriate classification should depend on the activity that is likely to be the predominant source or use of cash flows for the item. The new standard was effective for the Company on January 1, 2018. The adoption of this standard did not have a material impact on the Company's consolidated statements of cash flows upon adoption.

*ASU 2016-18, Statement of Cash Flows: Restricted Cash*

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows: Restricted Cash* ("ASU 2016-18"). The amendments in this update require that amounts generally described as restricted cash and restricted cash equivalents be included within cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. ASU 2016-18 was effective January 1, 2018. As a result of adopting ASU 2016-18, the Company includes its restricted cash balance in the cash, cash equivalents and restricted cash reconciliation of operating, investing and financing activities. The following table provides a reconciliation of cash, cash equivalents, and restricted cash within the statement of financial position that sum to the total of the same such amounts shown in the statement of cash flows:

(in thousands)	As of December 31,		
	2018	2017	2016
Cash and cash equivalents	\$ 402,579	\$ 758,505	\$ 278,887
Restricted cash included in receivables and other current assets	364	-	627
Restricted cash included in restricted cash and other non-current assets	14,156	13,763	13,763
Total cash, cash equivalents, and restricted cash shown in the statement of cash flows	\$ 417,099	\$ 772,268	\$ 293,277

*ASU 2017-09, Compensation - Stock Compensation (Topic 718): Scope Modification Accounting*

In May 2017, the FASB issued ASU 2017-09, *Compensation - Stock Compensation (Topic 718): Scope Modification Accounting*. The new standard is intended to reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718 to a change to the terms or conditions of a share-based payment award. The new standard was effective beginning January 1, 2018. The adoption of this standard did not have a material impact on the Company's financial position or results of operations upon adoption.

*ASU 2018-03, Technical Corrections and Improvements to Financial Instruments Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Liabilities*

In February 2018, the FASB issued ASU 2018-03, *Technical Corrections and Improvements to Financial Instruments Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Liabilities* ("ASU 2018-03"). The new standard amends the standard ASU 2016-01, *Financial Instruments Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities*, which was issued by the FASB in January 2016 and adopted by the Company effective January 1, 2018. This amendment simplifies the impairment assessment of equity investments without readily determinable fair values by requiring a qualitative assessment to identify impairment. In addition, it requires enhanced disclosures about investments. The Company adopted ASU 2018-03 effective July 1, 2018. The adoption of this standard did not have an impact on the Company's financial position or results of operations upon adoption.

*ASU 2018-07, Improvements to Nonemployee Share-Based Payment Accounting*

In June 2018, the FASB issued ASU 2018-07. The new standard simplifies the accounting for share-based payments to non-employees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The new standard will be effective beginning January 1, 2019 and early adoption is permitted. The Company early adopted ASU 2018-07 effective July 1, 2018 using a cumulative-effect adjustment as of the date of adoption. The impact of adopting this standard was not material.

Not yet adopted

*ASU 2016-02, Leases and ASU 2018-11, Leases, Targeting Improvements*

In February 2016, the FASB issued ASU 2016-02, *Leases*, ("ASU 2016-02"), which requires a lessee to recognize assets and liabilities on the balance sheet for most leases and changes many key definitions, including the definition of a lease. The new standard includes a short-term lease exception for leases with a term of 12 months or less, as part of which a lessee can make an accounting policy election not to recognize lease assets and lease liabilities. Lessees will continue to differentiate between finance leases (previously referred to as capital leases) and operating leases using classification criteria that are substantially similar to the previous guidance.

ASU 2016-02 will be effective beginning January 1, 2019 requiring the use of a modified retrospective transition approach applied at the beginning of the earliest comparative period presented in the financial statements. In July 2018, the FASB issued ASU 2018-11, *Leases, Targeted Improvements*, ("ASU 2018-11"), which contains certain amendments to ASU 2016-02 intended to provide relief in implementing the new standard. ASU 2018-11 provides registrants with an option to not restate comparative periods presented in the financial statements. The Company intends to elect this new transition approach using a cumulative-effect adjustment on the effective date of the standard, for which comparative periods will be presented in accordance with the previous guidance in ASC 840, *Leases*.

The Company is currently evaluating the potential impact ASU 2016-02 may have on its financial position, results of operations, and related footnotes. The Company expects it will elect to utilize the available package of practical expedients permitted under the transition guidance within the new standard, which does not require the reassessment of the following: i) whether existing or expired arrangements are or contain a lease, ii) the lease classification of existing or expired leases, and iii) whether previous initial direct costs would qualify for capitalization under the new lease standard. Additionally, the Company expects it will make an accounting policy election to keep leases with an initial term of 12 months or less off of its balance sheet. The Company's assessment will include, but is not limited to, evaluating the impact that this standard has on the lease of its corporate headquarters at 60 Binney Street in Cambridge, Massachusetts, its laboratory space in Seattle, Washington, its office space in Zug, Switzerland, its equipment leases, and its embedded leases associated with the Company's contract manufacturing agreements.

*ASU 2017-04, Intangibles - Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment*

In January 2017, the FASB issued ASU 2017-04, *Intangibles - Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment*. To address concerns over the cost and complexity of the two-step goodwill impairment test, the amendments in this ASU remove the second step of the test. An entity will instead apply a one-step quantitative test and record the amount of goodwill impairment as the excess of a reporting unit's carrying amount over its fair value, not to exceed the total amount of goodwill allocated to the reporting unit. The new guidance does not amend the optional qualitative assessment of goodwill impairment. The new standard will be effective beginning January 1, 2020 and early adoption is permitted with measurement dates on or after January 1, 2017. The adoption of this standard is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

*ASU 2017-08, Receivables - Nonrefundable Fees and Other Costs*

In April 2017, the FASB issued ASU 2017-08, *Receivables - Nonrefundable Fees and Other Costs* ("Subtopic 310-20"). The new standard amends the amortization period for certain purchased callable debt securities held at a premium by shortening the amortization period for the premium to the earliest call date. Subtopic 310-20 calls for a modified retrospective application under which a cumulative-effect adjustment will be made to retained earnings as of the beginning of the first reporting period in which the guidance is adopted. The new standard is effective beginning January 1, 2019. The adoption of this standard is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

*ASU 2018-02, Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*

In February 2018, the FASB issued ASU 2018-02, *Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*. The new standard allows for a reclassification from accumulated other comprehensive income to retained earnings for stranded tax effects resulting from the Tax Cuts and Jobs Act. The new standard will be effective beginning January 1, 2019. The adoption of this standard is not expected to have a material impact on the Company's financial position and results of operations upon adoption.

*ASU 2018-13, Fair Value Measurement (Topic 820): Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement*

In August 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement*, ("ASU 2018-13"). The new standard removes certain disclosures, modifies certain disclosures and adds additional disclosures related to fair value measurement. The new standard will be effective beginning January 1, 2020 and early adoption is permitted. The Company is currently evaluating the potential impact ASU 2018-13 may have on its disclosures upon adoption.

*ASU 2018-15, Intangibles-Goodwill and Other-Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*

In August 2018, the FASB issued ASU 2018-15, *Intangibles-Goodwill and Other-Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*, ("ASU 2018-15"). The amendments in this update align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use software license). The accounting for the service element of a hosting arrangement that is a service contract is not affected by the amendments in this update. The new standard will be effective beginning January 1, 2020 and early adoption is permitted. The amendments in this update should be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. The Company is currently evaluating the potential impact ASU 2018-15 may have on its financial position and results of operations upon adoption.

*ASU 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*

In November 2018, the FASB issued ASU 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*, ("ASU 2018-18"). The amendments in this update clarifies that certain transactions between collaborative arrangement participants should be accounted for as revenue when the collaborative arrangement participant is a customer in the context of a unit of account and precludes recognizing as revenue consideration received from a collaborative arrangement participant if the participant is not a customer. The new standard will be effective beginning January 1, 2020 and early adoption is permitted. The Company is currently evaluating the potential impact ASU 2018-18 may have on its financial position and results of operations upon adoption.

### 3. Marketable securities

The following table summarizes the marketable securities held at December 31, 2018 and 2017 (in thousands):

Description	Amortized Cost / Cost	Unrealized gains	Unrealized losses	Fair value
<b>December 31, 2018</b>				
U.S. government agency securities and treasuries	\$ 1,459,649	\$ 963	\$ (3,011 )	\$ 1,457,601
Certificates of deposit	9,080	-	-	9,080
Equity securities	20,017	2,150	-	22,167
Total	<u>\$ 1,488,746</u>	<u>\$ 3,113</u>	<u>\$ (3,011 )</u>	<u>\$ 1,488,848</u>
<b>December 31, 2017</b>				
U.S. government agency securities and treasuries	\$ 841,895	\$ -	\$ (3,579 )	\$ 838,316
Certificates of deposit	17,480	1	-	17,481
Total	<u>\$ 859,375</u>	<u>\$ 1</u>	<u>\$ (3,579 )</u>	<u>\$ 855,797</u>

No available-for-sale debt securities held as of December 31, 2018 or 2017 had remaining maturities greater than three years.

### 4. Fair value measurements

The following table sets forth the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2018 and 2017 (in thousands):

Description	Total	Quoted prices in active markets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
<b>December 31, 2018</b>				
Assets:				
Cash and cash equivalents	\$ 402,579	\$ 348,638	\$ 53,941	\$ -
Marketable securities:				
U.S. government agency securities and treasuries	1,457,601	-	1,457,601	-
Certificates of deposit	9,080	-	9,080	-
Equity securities	22,167	22,167	-	-
Total assets	<u>\$ 1,891,427</u>	<u>\$ 370,805</u>	<u>\$ 1,520,622</u>	<u>\$ -</u>
Liabilities:				
Contingent consideration	\$ 5,230	\$ -	\$ -	\$ 5,230
Total liabilities	<u>\$ 5,230</u>	<u>\$ -</u>	<u>\$ -</u>	<u>\$ 5,230</u>
<b>December 31, 2017</b>				
Assets:				
Cash and cash equivalents	\$ 758,505	\$ 758,505	\$ -	\$ -
Marketable securities:				
U.S. government agency securities	838,316	-	838,316	-
Certificates of deposit	17,481	-	17,481	-
Total assets	<u>\$ 1,614,302</u>	<u>\$ 758,505</u>	<u>\$ 855,797</u>	<u>\$ -</u>
Liabilities:				
Contingent consideration	\$ 2,231	\$ -	\$ -	\$ 2,231
Total liabilities	<u>\$ 2,231</u>	<u>\$ -</u>	<u>\$ -</u>	<u>\$ 2,231</u>

#### Cash and cash equivalents

The Company considers all highly liquid securities with original final maturities of 90 days or less from the date of purchase to be cash equivalents. As of December 31, 2018, cash and cash equivalents comprise funds in cash, U.S. treasury securities, U.S. government agency securities, and money market accounts. As of December 31, 2017, cash and cash equivalents comprise funds in cash and money market accounts.

### **Marketable securities**

The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity. At December 31, 2018 and 2017, the balance in the Company's accumulated other comprehensive loss was composed primarily of activity related to the Company's debt securities.

The aggregate fair value of debt securities held by the Company in an unrealized loss position for less than twelve months as of December 31, 2018 and 2017 was \$787.5 million and \$704.1 million, respectively. As of December 31, 2018, and 2017, there were \$315.3 million and \$134.4 million in securities held by the Company in an unrealized loss position for more than twelve months, respectively. The Company has the intent and ability to hold such securities until recovery. The Company determined that there was no material change in the credit risk of the above investments. As a result, the Company determined it did not hold any investments with an other-than-temporary impairment as of December 31, 2018 and 2017.

The Company holds equity securities with an aggregate fair value of \$22.2 million at December 31, 2018 within short-term marketable securities on its consolidated balance sheet. The Company has recorded a \$2.2 million unrealized gain during the year ended December 31, 2018 related to its equity securities, which is included in other income (expense), net on the consolidated statements of operations and comprehensive loss.

### **Contingent consideration**

On June 30, 2014, the Company acquired Pregen. In connection with the acquisition of Pregen, the Company recorded contingent consideration pertaining to the amounts potentially payable to Pregen's former equityholders. Contingent consideration is measured at fair value and is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The valuation of contingent consideration uses assumptions the Company believes would be made by a market participant. The Company assesses these estimates on an on-going basis as additional data impacting the assumptions is obtained. Future changes in the fair value of contingent consideration related to updated assumptions and estimates are recognized within the consolidated statements of operations and comprehensive loss.

Contingent consideration may change significantly as development progresses and additional data are obtained, impacting the Company's assumptions regarding probabilities of successful achievement of related milestones used to estimate the fair value of the liability and the timing in which they are expected to be achieved. In evaluating the fair value information, considerable judgment is required to interpret the market data used to develop the estimates. The estimates of fair value may not be indicative of the amounts that could be realized in a current market exchange. Accordingly, the use of different market assumptions and/or different valuation techniques could result in materially different fair value estimates.

The significant unobservable inputs used in the measurement of fair value of the Company's contingent consideration are probabilities of successful achievement of clinical and commercial milestones, the period in which these milestones are expected to be achieved ranging from 2021 to 2028 and discount rates ranging from 15.0% to 15.8%. Significant increases or decreases in any of these inputs would result in a significantly higher or lower fair value measurement.

The table below provides a roll-forward of fair value of the Company's contingent consideration obligations which include Level 3 inputs (in thousands):

	<b>Year ended December 31,</b>	
	<b>2018</b>	<b>2017</b>
Beginning balance	\$ 2,231	\$ 7,756
Additions	-	-
Changes in fair value	2,999	(525 )
Payments	-	(5,000 )
Ending balance	\$ 5,230	\$ 2,231

As of December 31, 2018 and 2017, the remaining \$5.2 million, and \$2.2 million, respectively, of contingent consideration obligation is reflected as a non-current liability in the consolidated balance sheet. A \$5.0 million preclinical milestone was achieved and paid to the former equityholders of Pregen in the year ended December 31, 2017. Please refer to Note 8, "Commitments and contingencies," for further information.

## 5. Property, plant and equipment, net

Property, plant and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2018	2017
Land	\$ 1,210	\$ 1,210
Building	180,094	164,414
Computer equipment and software	6,365	5,134
Office equipment	5,584	4,478
Laboratory equipment	35,693	24,914
Leasehold improvements	183	116
Construction-in-progress	<u>46,669</u>	<u>15,189</u>
Total property, plant and equipment	275,798	215,455
Less accumulated depreciation and amortization	(29,176)	(15,849)
Property, plant and equipment, net	<u>\$ 246,622</u>	<u>\$ 199,606</u>

In November 2017, the Company acquired a manufacturing facility, which is in the process of construction, in Durham, North Carolina for the future manufacture of lentiviral vector for the Company's gene and cell therapies. Construction-in-progress as of December 31, 2018, and 2017, includes \$40.4 million and \$12.9 million related to the North Carolina manufacturing facility, respectively.

As of December 31, 2018, and 2017, total property, plant and equipment includes \$168.1 million, and \$164.4 million, respectively, related to the Company's headquarters at 60 Binney Street in Cambridge, Massachusetts, of which \$156.0 million was incurred by the landlord at both dates.

Depreciation and amortization expense related to property, plant and equipment was \$13.4 million, \$9.8 million, and \$5.9 million for the years ended December 31, 2018, 2017, and 2016, respectively. Please refer to Note 8, "Commitments and contingencies," for further information.

## 6. Restricted cash and other non-current assets

### Restricted cash

As of December 31, 2018, and 2017, the Company maintained letters of credit of \$14.5 million, and \$13.8 million, respectively, which are collateralized with a bank account at a financial institution in accordance with the agreement and consisted of the following:

	As of December 31, 2018	As of December 31, 2017
(in thousands)		
60 Binney Street lease	\$ 13,763	\$ 13,763
Other leases	757	-
Total restricted cash	<u>\$ 14,520</u>	<u>\$ 13,763</u>

Subject to the terms of the 60 Binney Street Lease agreement and certain reduction requirements specified therein, including market capitalization requirements, this amount may decrease by \$1.5 million on the fourth, fifth and sixth anniversaries of the date the Company occupies the building.

### Other non-current assets

In August 2018, the Company entered into a license and collaboration agreement with a third-party collaborator and paid a non-refundable, non-creditable upfront payment of \$20.0 million, \$14.5 million of which was recorded as prepaid research and development services and the remaining \$5.5 million of which was expensed within research and development expense in the third quarter of 2018, as this payment represented an access fee for technology that has no clear alternate future use under ASC 730-10, *Research and Development*. The prepaid research and development services will be recognized over a five-year term based on the proportion of effort incurred by the third-party collaborator as a percentage of total effort expected to be expended. The prepaid research and development services balance is included in receivables and other current assets and restricted cash and other non-current assets in the consolidated balance sheet as of December 31, 2018.

## 7. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consist of the following (in thousands):

	As of December 31,	
	<u>2018</u>	<u>2017</u>
Employee compensation	\$ 28,567	\$ 19,657
Accrued manufacturing costs	21,618	8,480
Accrued clinical and contract research organization costs	11,891	8,082
Accrued license and milestone fees	7,739	4,584
Accrued professional fees	1,830	1,402
Other accrued goods and services	25,051	12,971
Financing lease obligation, current portion	1,424	1,051
Other	1,273	838
<b>Total accrued expenses and other current liabilities</b>	<b>\$ 99,393</b>	<b>\$ 57,065</b>

## 8. Commitments and contingencies

### *Operating lease commitments*

On June 3, 2016, the Company entered into a manufacturing agreement for the future commercial production of the Company's Lenti-D and LentiGlobin product candidates with a contract manufacturing organization. Under this 12 year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, the Company was required to pay \$12.5 million upon the achievement of certain contractual milestones, and may pay up to \$8.0 million in additional contractual milestones if the Company elects its option to lease additional suites. The Company paid \$5.0 million for the achievement of the first and second contractual milestones during 2016 and paid \$5.5 million for the third and fourth contractual milestones achieved during 2017. In March 2018, \$1.5 million of the possible \$2.0 million related to the fifth contractual milestone was achieved and was paid in the second quarter of 2018. Given that construction was completed in March 2018, beginning in April 2018 the Company will pay \$5.1 million per year in fixed suite fees as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services, and may pay additional suite fees if it elects its option to reserve or lease additional suites. The Company may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. The Company concluded that this agreement contains an embedded lease as the suites are designated for the Company's exclusive use during the term of the agreement. The Company concluded that it is not the deemed owner during construction nor is it a capital lease under ASC 840-10, *Leases - Overall*. As a result, the Company accounts for the agreement as an operating lease and expenses the rental payments on a straight-line basis over the non-cancellable term of the embedded lease.

On November 18, 2016, the Company entered into an agreement for future clinical and commercial production of the Company's LentiGlobin and Lenti-D gene therapy drug products with a contract manufacturing organization at an existing facility. The term of the agreement is five years with a three year renewal at the mutual option of each party. Under the agreement, the Company is required to pay an up-front fee of €3.0 million, €2.0 million of which was paid in the fourth quarter of 2016 and €1.0 million of which was paid in the third quarter of 2018, and annual maintenance and production fees of up to €9.8 million, depending on its production needs. The Company may terminate this agreement with twelve months' notice and a one-time termination fee. The Company concluded that this agreement contains an embedded lease as the clean rooms are designated for the Company's exclusive use during the term of the agreement and determined that it is not a capital lease under ASC 840-10, *Leases - Overall*. As a result, the Company accounts for the agreement as an operating lease and expenses the rental payments on a straight-line basis over the non-cancellable term of the embedded lease.

### **60 Binney Street Lease commitments**

On September 21, 2015, the Company entered into a lease agreement for office and laboratory space located in a building (the “Building”) at 60 Binney Street, Cambridge, Massachusetts (the “60 Binney Street Lease”) to become its new corporate headquarters. Under the terms of the 60 Binney Street Lease, starting on October 1, 2016, the Company leases approximately 253,108 square feet of office and laboratory space at \$72.50 per square foot per year, or \$18.4 million per year in base rent, which is subject to scheduled annual rent increases of 1.75% plus certain operating expenses and taxes. The Company also executed a \$9.2 million letter of credit upon signing the 60 Binney Street Lease, which was required to be collateralized with a bank account at a financial institution in accordance with the 60 Binney Street Lease agreement. This letter of credit was increased to \$13.8 million during the third quarter of 2016 as required under the terms of the lease. Subject to the terms of the lease and certain reduction requirements specified therein, including market capitalization requirements, this amount may decrease back to \$9.2 million over time. The 60 Binney Street Lease will continue until March 31, 2027. Pursuant to a work letter entered into in connection with the 60 Binney Street Lease, the landlord will contribute an aggregate of \$42.4 million toward the cost of construction and tenant improvements for the Building. The purpose of the 60 Binney Street Lease was to replace the Company’s previously leased premises at 150 Second Street and 215 First Street in Cambridge, Massachusetts, both of which were fully exited in the first half of 2017. The Company has the option to extend the 60 Binney Street Lease for two successive five-year terms. The Company occupied the Building beginning on March 27, 2017.

Because the Company is involved in the construction project, including having responsibility to pay for a portion of the costs of finish work and mechanical, electrical, and plumbing elements of the Building, among other items, the Company is deemed for accounting purposes to be the owner of the Building during the construction period. Accordingly, construction costs that have been incurred by the landlord directly or indirectly through reimbursement to the Company as part of its tenant improvement allowance have been recorded as an asset in “Property, plant and equipment, net” with a related financing obligation in “Accrued expenses and other current liabilities” and “Financing lease obligation, net of current portion” on the Company’s consolidated balance sheets. Tenant improvement costs that are reimbursable by the landlord and have not yet been paid to the Company are recorded in “Tenant improvements receivable” on the Company’s consolidated balance sheets. Tenant improvement costs that are not reimbursable by the landlord are recorded in “Property, plant and equipment, net” on the Company’s consolidated balance sheets.

The Company evaluated the 60 Binney Street Lease upon occupancy on March 27, 2017 and determined that the 60 Binney Street Lease did not meet the criteria for “sale-leaseback” treatment. This determination was based on, among other things, the Company’s continuing involvement with the property in the form of non-recourse financing to the lessor. Accordingly, upon occupancy, the Company commenced depreciating the portion of the building in service over a useful life of 40 years and incurred interest expense related to the financing obligation of \$15.5 million, and \$11.4 million, for the years ended December 31, 2018 and 2017, respectively. The Company made \$1.0 million and \$0.6 million in principal payments, which are included in operating expense, for the years ended December 31, 2018 and 2017, respectively.

The Company bifurcates its lease payments pursuant to the 60 Binney Street Lease into (i) a portion that is allocated to the Building and (ii) a portion that is allocated to the land on which the Building is located, which is recorded as rental expense. The Company began making lease payments pursuant to the 60 Binney Street Lease in March 2017. The portion of the lease obligation allocated to the land is treated for accounting purposes as an operating lease that commenced upon execution of the 60 Binney Street Lease in September 2015. During the years ended December 31, 2018, 2017 and 2016, the Company recognized \$1.9 million, \$1.9 million, and \$1.9 million of rental expense attributable to the land, respectively.

As of December 31, 2018, future minimum commitments under the 60 Binney Street Lease and facility operating leases were as follows (in thousands):

<b>Years ended December 31,</b>	<b>60 Binney Street lease</b>	<b>Other operating leases (1)</b>	<b>Total lease commitments</b>
2019	\$ 18,974	\$ 17,511	\$ 36,485
2020	19,306	18,727	38,033
2021	19,643	18,777	38,420
2022	19,987	13,332	33,319
2023	20,337	13,384	33,721
2024 and thereafter	68,551	29,313	97,864
<b>Total minimum lease payments</b>	<b>\$ 166,798</b>	<b>\$ 111,044</b>	<b>\$ 277,842</b>

(1) Includes the lease of the Company’s lab and office space in Seattle, Washington, office space in Zug, Switzerland and two embedded operating leases at contract manufacturing organizations.

For the 60 Binney Street Lease, the table above sets forth the future minimum rental payments that the Company is obligated to pay, including amounts reflected on the consolidated balance sheet as part of the balance under the caption “Accrued expenses and other current liabilities” and “Financing lease obligation, net of current portion.” The Company commenced rental payments in April 2017.

Rent expense is calculated on a straight-line basis over the term of the lease. Rent expense recognized under all leases, including additional rent charges for utilities, parking, maintenance, and real estate taxes, and including rental expense attributable to the 60 Binney Street Lease land was \$9.8 million, \$9.0 million, and \$8.3 million for the years ended December 31, 2018, 2017 and 2016, respectively.

#### ***Contingent consideration related to business combinations***

On June 30, 2014, the Company acquired Pregen. During 2017, one milestone under the Stock Purchase Agreement was achieved, which resulted in a \$5.0 million payment to the former equityholders of Pregen during 2017. During 2016, two milestones were achieved, which resulted in a \$5.0 million payment to the former equityholders of Pregen. The Company may be required to make up to an additional \$120.0 million in remaining future contingent cash payments to the former equityholders of Pregen upon the achievement of certain clinical and commercial milestones related to the Pregen technology, of which \$20.1 million relates to clinical milestones and \$99.9 million relates to commercial milestones. In accordance with accounting guidance for business combinations, contingent consideration liabilities are required to be recognized on the consolidated balance sheets at fair value. Estimating the fair value of contingent consideration requires the use of significant assumptions primarily relating to probabilities of successful achievement of certain clinical and commercial milestones, the expected timing in which these milestones will be achieved and discount rates. The use of different assumptions could result in materially different estimates of fair value. See Note 4, “*Fair value measurements*,” for additional information.

#### ***Other funding commitments***

The Company is party to various agreements, principally relating to licensed technology, that require future payments relating to milestones not met at December 31, 2018 and December 31, 2017 or royalties on future sales of specified products, which includes the collaboration agreement entered into with Regeneron Pharmaceuticals, Inc. (“Regeneron”) during the year ended December 31, 2018. Additionally, the Company is party to various contracts with contract research organizations and contract manufacturers that generally provide for termination on notice, with the exact amounts in the event of termination to be based on the timing of the termination and the terms of the agreement. Please refer to Note 10, “*Collaborative Arrangements*,” for further information on the collaboration agreement with Regeneron.

Based on our development plans as of December 31, 2018, we may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with our collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company’s financial statements and are excluded from the table below.

The Company has various manufacturing development and license agreements to support clinical and commercial product needs. The Company incurred \$44.0 million of expense related to these agreements in 2018. The following table presents non-cancelable contractual obligations arising from these arrangements:

<b>Years ended December 31,</b>	<b>Purchase commitment</b>
2019	\$ 69,827
2020	74,529
2021	14,358
2022	24,311
2023	25,040
2024 and thereafter	25,792
Total purchase commitments	<u>\$ 233,857</u>

The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company indemnifies, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company's business partners. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is unlimited. The Company has never incurred costs to defend lawsuits or settle claims related to these indemnification agreements.

#### **9. Common stock and preferred stock**

The Company is authorized to issue 125.0 million shares of common stock. Holders of common stock are entitled to one vote per share. Holders of common stock are entitled to receive dividends, if and when declared by the Company's Board of Directors, and to share ratably in the Company's assets legally available for distribution to the Company's shareholders in the event of liquidation. Holders of common stock have no preemptive, subscription, redemption or conversion rights. As of December 31, 2018, and 2017, the Company had 54.7 million and 49.4 million shares of common stock issued and outstanding, respectively.

In December 2016, the Company sold 3.3 million shares of common stock through an underwritten public offering at a price of \$76.00 per share for aggregate net proceeds of \$234.7 million. In June 2017, the Company sold 4.4 million shares of common stock (inclusive of 0.6 million shares of common stock sold by the Company pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$105.00 per share for aggregate net proceeds of \$436.8 million. In December 2017, the Company sold 3.2 million shares of common stock (excluding any shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$185.00 per share for aggregate net proceeds of \$569.8 million.

In January 2018, the Company sold 0.3 million shares of common stock pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the December 2017 underwritten public offering at a price of \$185.00 per share for aggregate net proceeds of \$48.7 million. In July 2018, the Company sold 3.9 million shares of common stock (excluding any shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$162.50 per share for aggregate net proceeds of \$600.6 million. In August 2018, the Company sold 0.4 million shares of common stock to Regeneron in connection with a collaboration arrangement at a price of \$238.10 per share for aggregate net proceeds of \$100.0 million, of which \$45.5 million was attributed to a prepayment of joint research activities.

The Company is authorized to issue 5.0 million shares of preferred stock in one or more series and to fix the powers, designations, preferences and relative participating option or other rights thereof, including dividend rights, conversion rights, voting rights, redemption terms, liquidation preferences and the number of shares constituting any series, without any further vote or action by the Company's shareholders. As of December 31, 2018 and 2017, the Company had no shares of preferred stock issued or outstanding.

#### *Reserved for future issuance*

The Company has reserved for future issuance the following number of shares of common stock (in thousands):

	<u>As of December 31,</u>	
	<u>2018</u>	<u>2017</u>
Options to purchase common stock	4,643	3,755
Restricted stock units	931	477
2013 Stock Option and Incentive Plan	1,458	1,550
2013 Employee Stock Purchase Plan	172	188
	<u>7,204</u>	<u>5,970</u>

#### **10. Collaborative arrangements**

To date, the Company's collaboration revenue has been generated from its collaboration arrangement with Celgene, which was originally entered into in March 2013 and was subsequently amended in June 2015, and from its collaboration arrangement with Regeneron, as further described below.

## **Celgene**

### ***Celgene Original Collaboration Agreement***

On March 19, 2013, the Company entered into a Master Collaboration Agreement (the “Celgene Collaboration Agreement”) with Celgene to discover, develop and commercialize potentially disease-altering gene therapies in oncology. The collaboration is focused on applying gene therapy technology to genetically modify a patient’s own T cells, known as chimeric antigen receptor, or CAR T cells, to target and destroy cancer cells. Additionally, on March 19, 2013, the Company entered into a Platform Technology Sublicense Agreement (the “Sublicense Agreement”) with Celgene pursuant to which the Company obtained a sublicense to certain intellectual property from Celgene, originating under Celgene’s license from Baylor College of Medicine, for use in the collaboration.

Under the terms of the Celgene Collaboration Agreement, the Company received a \$75.0 million up-front, non-refundable cash payment. The Company was responsible for conducting discovery, research and development activities through completion of phase 1 clinical studies, if any, during the initial term of the Celgene Collaboration Agreement, or three years. The collaboration is governed by a joint steering committee (“JSC”) formed by an equal number of representatives from the Company and Celgene. The JSC, among other activities, reviews the collaboration program, reviews and evaluates product candidates and approves regulatory plans. In addition to the JSC, the Celgene Collaboration Agreement provides that the Company and Celgene each appoint representatives to a patent committee, which is responsible for managing the intellectual property developed and used during the collaboration.

### ***Celgene Amended Collaboration Agreement***

On June 3, 2015, the Company and Celgene amended and restated the Collaboration Agreement (the “Amended Celgene Collaboration Agreement”). Under the Amended Celgene Collaboration Agreement, the parties narrowed the focus of the collaboration to exclusively work on anti- B-cell maturation antigen (“BCMA”) product candidates for a new three-year term. In connection with the Amended Celgene Collaboration Agreement, the Company received an up-front, one-time, non-refundable, non-creditable payment of \$25.0 million to fund research and development under the collaboration. The collaboration will continue to be governed by the JSC. Under the terms of the Amended Celgene Collaboration Agreement, for up to two product candidates selected for development under the collaboration, the Company is responsible for conducting and funding all research and development activities performed up through completion of the initial phase 1 clinical study of such product candidates.

On a product candidate-by-product candidate basis, up through a specified period following enrollment of the first patient in an initial phase 1 clinical study for such product candidate (the “Option Period”), the Company has granted Celgene an option to obtain an exclusive worldwide license to develop and commercialize such product. Following Celgene’s license of each product candidate, the Company is entitled to elect to co-develop and co-promote each product candidate in the U.S.

### ***Celgene bb2121 License Agreement***

On February 10, 2016, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb2121, the first product candidate under the Amended Celgene Collaboration Agreement, pursuant to an executed license agreement (“bb2121 License Agreement”) entered into by the parties on February 16, 2016 and paid the associated \$10.0 million option fee. Pursuant to the bb2121 License Agreement, Celgene is responsible for development and related funding of bb2121 after the substantial completion of the phase 1 clinical trial. The Company is responsible for the manufacture of vector and associated payload throughout development and upon Celgene’s request, commercialization, the costs of which are reimbursed by Celgene in accordance with the terms of the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement, as further described below. Celgene is responsible for the manufacture of drug product throughout development and commercialization.

### ***Celgene bb2121 Co-Development, Co-Promote and Profit Share Agreement***

On March 28, 2018, the Company elected to co-develop and co-promote bb2121 within the U.S. pursuant to the execution of the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement (“bb2121 CCPS”). The responsibilities of the parties remain unchanged from those under the bb2121 License Agreement, however, the Company will share equally in all profits and losses relating to developing, commercializing and manufacturing bb2121 within the U.S. and has the right to participate in the development and promotion of bb2121 in the U.S. Celgene is responsible for the costs incurred to manufacture vector and associated payload for use outside of the U.S., plus a markup. Under the bb2121 CCPS, the Company may receive up to \$70.0 million in development milestone payments for the first indication to be addressed by the bb2121 product candidate, with the ability to obtain additional milestone payments for a second indication and modified licensed products. In addition, to the extent bb2121 is commercialized, the Company is entitled to receive tiered royalty payments ranging from the mid-single digits to low-teens based on a percentage of net sales generated outside of the U.S., subject to certain reductions.

***Celgene bb21217 License Agreement***

On September 22, 2017, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb21217, the second product candidate under the Amended Celgene Collaboration Agreement, pursuant to an executed license agreement (“bb21217 License Agreement”) entered into by the parties on September 28, 2017 and paid the Company an option fee of \$15.0 million. Pursuant to the bb21217 License Agreement, Celgene is responsible for development and related funding of bb21217 after the substantial completion of the on-going phase 1 clinical trial. The Company is responsible for the manufacture of vector and associated payload throughout development and, upon Celgene’s request, commercialization. Expenses incurred by the Company are fully reimbursable by Celgene at cost plus a mark-up. Throughout both development and commercialization, Celgene is responsible for the manufacture of drug product.

The Company currently expects it will exercise its option to co-develop and co-promote bb21217 within the U.S. The Company’s election to co-develop and co-promote bb21217 must be made by the substantial completion of the on-going phase 1 clinical trial of bb21217. If elected, the Company expects the responsibilities of the parties to remain largely unchanged, however, the Company expects it will share equally in all profits and losses relating to developing, commercializing and manufacturing bb21217 within the U.S. and to have the right to participate in the development and promotion of bb21217 in the U.S. Celgene would be responsible for the costs incurred to manufacture vector and associated payload for use outside of the U.S., plus a markup. Under this scenario, the Company expects to receive, per product, up to \$70.0 million in development milestone payments for the first indication to be addressed by the bb21217 product candidate, with the ability to obtain additional milestone payments for a second indication and modified licensed products. In addition, to the extent bb21217 is commercialized, the Company would be entitled to receive tiered royalty payments ranging from the mid-single digits to low-teens based on a percentage of net sales generated outside of the U.S., subject to certain reductions.

In the event the Company does not exercise its option to co-develop and co-promote bb21217, the Company will receive an additional fee in the amount of \$10.0 million. Under this scenario, the Company may be eligible to receive up to \$10.0 million in clinical milestone payments, up to \$117.0 million in regulatory milestone payments, and up to \$78.0 million in commercial milestone payments. In addition, to the extent bb21217 is commercialized, the Company would be entitled to receive tiered royalty payments ranging from the mid-single digits to low-teens based on a percentage of net sales, subject to certain reductions.

***Accounting Analysis - bb2121***

The Company has elected to use a practical expedient within Topic 606 that allows entities to reflect the aggregate effect of all contract modifications when identifying the satisfied and unsatisfied performance obligations for contracts that were modified prior to Topic 606 adoption. Celgene’s option to in-license the first product candidate, bb2121, under the arrangement was considered a material right at the time the Amended Celgene Collaboration Agreement was executed in June 2015 given the product candidate had been formally nominated by the JSC and that substantially all investigational new drug application, or IND, enabling activities had been completed by that time. In making this determination, the Company also considered the option price relative to the value of the underlying license. Celgene’s exercise of this material right in February 2016 was determined to represent a contract modification and represents the last contract modification prior to the adoption of Topic 606. As a result, the Celgene Collaboration Agreement, Amended Celgene Collaboration Agreement, and bb2121 CCPS are combined for accounting purposes and treated as a single arrangement. As of February 2016, Celgene’s option to license an additional product candidate under the collaboration did not represent a material right due primarily to the significant uncertainty regarding whether any additional product candidates would be identified under the Amended Celgene Collaboration Agreement. Therefore, the license to the Company’s second product candidate, bb21217, which was executed in September 2017, is accounted for as a separate contract. Refer below for discussion of the bb21217 accounting analysis.

As of the February 2016 contract modification date, the Company concluded the arrangement contained the following promised goods and services: (i) research and development services, (ii) a license to the first product candidate, bb2121, and (iii) manufacture of vectors and associated payload for incorporation into bb2121 through development. The Company determined that the manufacture of commercial vector represents an option to acquire additional goods and services that is not representative of a material right. In addition, at that time Celgene had not exercised its option to purchase any commercial vector. Accordingly, the manufacture of commercial vector is not considered to be a performance obligation at this time.

The Company concluded that the research and development services are distinct from the other promised goods and services under the arrangement given that Celgene can benefit from the research and development services on their own and such services are distinct within the context of the contract. Thus, such services are considered to be a separate performance obligation. The Company concluded that the license to bb2121 is not distinct from the vector manufacturing services because the manufacturing is essential to the use of the license. Accordingly, these two promised goods and services are considered a single combined performance obligation.

*bb2121 transaction price*

The following tables summarize the total transaction price, the allocation of the total transaction price to the identified performance obligations under the arrangement, and the amount of the transaction price unsatisfied as of December 31, 2018:

(in thousands)	<b>bb2121 transaction price as of December 31, 2018</b>	
Up-front non-refundable payment - Celgene Collaboration Agreement	\$ 75,000	
Up-front non-refundable payment - Amended Celgene Collaboration Agreement	25,000	
bb2121 license fee - bb2121 License Agreement	10,000	
Estimated variable consideration	85,723	
	\$ 195,723	
(in thousands)	<b>Allocation of transaction price to performance obligations</b>	<b>Transaction price unsatisfied as of December 31, 2018</b>
bb2121 research and development services	\$ 38,647	\$ -
bb2121 license and manufacturing services	157,076	50,599
	\$ 195,723	\$ 50,599

The estimated variable consideration of \$85.7 million relates to the estimated reimbursement from Celgene for the manufacture of vectors and associated payload through development. The total transaction price has been allocated to the performance obligations identified based on a relative SSP basis. The Company estimated the SSP of the license after considering potential future cash flows under the license. The Company then discounted these probability-weighted cash flows to their present value. The Company estimated the SSP of each of the research and development services and manufacturing services to be provided based on the Company's estimated cost of providing the services plus an applicable profit margin commensurate with observable market data for similar services.

All of the clinical and regulatory milestones are fully constrained. As part of its evaluation of the constraint, the Company considered numerous factors, including the fact that achievement of the milestones is outside the control of the Company and contingent upon the future success of clinical trials, the licensee's efforts, or the receipt of regulatory approval. Any consideration related to sales-based milestones (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to Celgene and therefore are recognized at the later of when the performance obligation is satisfied, or the related sales occur. The Company re-evaluates the transaction price, including its estimated variable consideration included in the transaction price and all constrained amounts, at each reporting period and as uncertain events are resolved or other changes in circumstances occur.

*bb2121 research and development services*

The Company allocated \$38.6 million of the transaction price to the research and development services. The Company satisfied this performance obligation as the research and development services were performed. The Company determined that the period of performance of the research and development services was three years through projected initial phase 1 clinical study substantial completion, or through May 2018. The Company recognized revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred. Although the Company fully satisfied this performance obligation during the second quarter of 2018, any changes to the total transaction price following the completion of this performance obligation in May 2018 will be allocated to the performance obligations under the arrangement based on a relative SSP basis and therefore the allocation of any changes to the total transaction price may impact the revenue recognized for this performance obligation in the period of change.

The following table summarizes the revenue recognized related to the bb2121 research and development services for the years ended December 31, 2018, 2017, and 2016:

(in thousands)	For the years ended December 31,		
	2018 (1)	2017 (1)	2016 (1)
bb2121 research and development services			
revenue	\$ 5,751	\$ 6,208	\$ 6,155
	<u>\$ 5,751</u>	<u>\$ 6,208</u>	<u>\$ 6,155</u>

(1) As noted in Note 2, “*Summary of significant accounting policies and basis of presentation*,” the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed in the table above pertaining to prior periods are presented under previous accounting guidance and are therefore not comparable to the amounts recorded in the current period under Topic 606.

#### *bb2121 license and manufacturing services*

The Company allocated \$157.1 million of the transaction price to the combined unit of accounting which consists of the license and manufacture of vectors and associated payload for incorporation into bb2121.

The Company accounts for its vector manufacturing services for development in the U.S. and Celgene’s U.S. development efforts within the scope of ASC 808 given that both parties are active participants in the activities and both parties are exposed to significant risks and rewards dependent on the commercial success of the activities. The Company recognizes collaboration revenue for its U.S. manufacturing services by analogy to Topic 606. The portion of Celgene’s U.S. development costs that the Company is responsible for are recognized as a reduction to its collaboration revenues, or, if in excess of such revenues in a given quarter, the excess is recorded as research and development expense.

Revenue recognition for the combined unit of accounting commenced during the first quarter of 2017. The Company recognizes revenue associated with the combined unit of accounting using the proportional performance method, as the Company will satisfy this performance obligation as the manufacturing services are performed through development. In using this method, the Company estimated its development plan for bb2121, including expected demand from Celgene, and the costs associated with the manufacture of vectors and associated payload for incorporation into bb2121. On a quarterly basis, the Company determines the proportion of effort incurred as a percentage of total effort it expects to expend. This ratio is applied to the transaction price, which includes variable consideration, allocated to the combined performance obligation consisting of the bb2121 license and manufacturing services. Management has applied significant judgment in the process of developing its budget estimates and any changes to these estimates will be recognized in the period in which they change as a cumulative catch up.

The following table summarizes the net collaboration revenue recognized or expense incurred related to the combined performance obligation for the license and vector manufacturing of bb2121 in the U.S. for the years ended December 31, 2018, 2017, and 2016:

bb2121 license and manufacturing services - U.S. (in thousands)	For the years ended December 31,		
	2018 (2)	2017 (2)	2016 (2)(3)
ASC 808 bb2121 license and manufacturing revenue - U.S. (1)	\$ 6,255	\$ 4,905	\$ -
ASC 808 bb2121 license and manufacturing research and development expense - U.S. (1)	\$ 8,689	\$ 3,037	\$ -

(1) As noted above, the calculation of collaboration revenue or research and development expense to be recognized for the Company’s combined performance obligation for its license and vector manufacturing of bb2121 in the U.S. is performed on a quarterly basis. The calculation is independent of previous activity, which may result in fluctuations between revenue and expense recognition period over period, depending on the varying extent of effort performed by each party during the period.

(2) As noted in Note 2, “*Summary of significant accounting policies and basis of presentation*,” the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed in the table above pertaining to prior periods are presented under previous accounting guidance and are therefore not comparable to the amounts recorded in the current period under Topic 606.

(3) Revenue recognition for the bb2121 license and manufacturing services for Celgene commenced in 2017 and as such there were no amounts recognized in the consolidated statement of operations in 2016.

Revenue related to the combined unit of accounting for its non-US license and vector manufacturing services is accounted for in accordance with Topic 606. The following table summarizes the revenue recognized related to the combined unit of accounting for the bb2121 non-US license and vector manufacturing services for the years ended December 31, 2018, 2017, and 2016:

	For the years ended December 31,		
	2018 (1)	2017 (1)	2016 (1)(2)
bb2121 license and manufacturing services - outside of U.S. (in thousands)			
ASC 606 license and manufacturing revenue - outside of U.S.	\$ 35,900	\$ 10,372	\$ -

- (1) As noted in Note 2, "Summary of significant accounting policies and basis of presentation," the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed in the table above pertaining to prior periods are presented under previous accounting guidance and are therefore not comparable to the amounts recorded in the current period under Topic 606.
- (2) Revenue recognition for the bb2121 license and manufacturing services for Celgene commenced in 2017 and as such there were no amounts recognized in the consolidated statement of operations in 2016.

As of December 31, 2018, the aggregate amount of the transaction price allocated to the combined performance obligation, which consists of the bb2121 license and manufacturing services, that is unsatisfied, or partially unsatisfied, is \$50.6 million, which the Company expects to recognize as revenue as manufacturing services are provided through the remaining development period which is estimated to be through 2020. As of December 31, 2018, the Company had \$23.0 million of deferred revenue associated with the combined performance obligation consisting of the bb2121 license and manufacturing services.

#### ***Accounting Analysis - bb2121***

On September 22, 2017, Celgene exercised its option to obtain an exclusive worldwide license to develop and commercialize bb2121, the second optioned product candidate, pursuant to the bb2121 License Agreement entered into by the parties on September 28, 2017. The bb2121 License Agreement is considered a separate contract for accounting purposes as the option to obtain an exclusive worldwide license to develop and commercialize bb2121, or any other product candidate, was not considered a material right to Celgene at the time the practical expedient was applied. The Company made this evaluation after considering the significant uncertainty at that time regarding whether any additional product candidates would be identified under the Amended Celgene Collaboration Agreement. In particular, the Company considered that bb2121 had not been formally nominated as a product candidate under the collaboration at that time, primarily due to a lack of pre-clinical data as well as uncertainty surrounding the ability to successfully complete various IND-enabling activities.

At contract inception, the Company concluded that the arrangement contained the following promised goods and services: (i) research and development services, (ii) a license to the second product candidate, bb2121, and (iii) manufacture of vectors and associated payload for incorporation into bb2121 through development. The Company determined that the manufacture of commercial vector represents an option to acquire additional goods and services that is not representative of a material right. In addition, at this time Celgene has not exercised its option to purchase any commercial vector. Accordingly, the manufacture of commercial vector is not considered to be a performance obligation at this time.

The Company concluded that the research and development services are distinct from the other promised goods and services under the arrangement given that Celgene can benefit from the research and development services on their own and such services are distinct within the context of the contract. Thus, such services are considered to be a separate performance obligation. Similar to bb2121, the Company concluded that the license to bb2121 is not distinct from the vector manufacturing services because the manufacturing is essential to the use of the license. Accordingly, these two promised goods and services are considered a single combined performance obligation.

#### ***bb2121 transaction price***

The following tables summarize the total transaction price, the allocation of the total transaction price to the identified performance obligations under the arrangement, and the amount of the transaction price unsatisfied as of December 31, 2018:

	bb2121 transaction price as of December 31, 2018
(in thousands)	
bb2121 license fee - bb2121 License Agreement	\$ 15,000
Estimated variable consideration	26,687
	<hr/>
	\$ 41,687

(in thousands)	Allocation of transaction price to performance obligations	Transaction price unsatisfied as of December 31, 2018
bb21217 research and development services	\$ 5,444	\$ 1,839
bb21217 license and manufacturing services	36,243	36,243
	<u>\$ 41,687</u>	<u>\$ 38,082</u>

The estimated variable consideration of \$26.7 million relates to reimbursement from Celgene for the manufacturing services during development. The total transaction price has been allocated to the performance obligations identified based on a relative SSP basis. The Company estimated the SSP of the license after considering potential future cash flows under the license. The Company then discounted these probability-weighted cash flows to their present value. The Company estimated the SSP of each of the research and development services and manufacturing services to be provided based on the Company's estimated cost of providing the services plus an applicable profit margin commensurate with observable market data for similar services.

All of the clinical and regulatory milestones are fully constrained. As part of its evaluation of the constraint, the Company considered numerous factors, including the fact that achievement of the milestones is outside the control of the Company and contingent upon the future success of its clinical trials, the licensee's efforts, or the receipt of regulatory approval. Any consideration related to sales-based milestones (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to Celgene and therefore are recognized at the later of when the performance obligation is satisfied, or the related sales occur. The Company re-evaluates the transaction price, including its estimated variable consideration included in the transaction price and all constrained amounts, each reporting period and as uncertain events are resolved or other changes in circumstances occur.

#### *bb21217 research and development services*

The Company allocated \$5.4 million of the transaction price to the research and development services. The Company will satisfy this performance obligation as the research and development services are performed. The Company determined that the period of performance of the research and development services was two years through projected initial phase 1 clinical study substantial completion, or through September 2019. The Company recognizes revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred.

The following table summarizes the revenue recognized related to the bb21217 research and development services for the years ended December 31, 2018, 2017, and 2016

(in thousands)	For the years ended December 31,		
	2018 (1)	2017 (1)	2016 (1)(2)
bb21217 research and development services revenue	\$ 2,884	\$ 721	\$ -
	<u>\$ 2,884</u>	<u>\$ 721</u>	<u>\$ -</u>

- (1) As noted in Note 2, "Summary of significant accounting policies and basis of presentation," the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed in the table above pertaining to prior periods are presented under previous accounting guidance and are therefore not comparable to the amounts recorded in the current period under Topic 606.
- (2) Celgene in-licensed bb21217 in September 2017 and as such there were no amounts recognized in the consolidated statement of operations in 2016.

As of December 31, 2018, the aggregate amount of the transaction price allocated to the bb21217 research and development services performance obligation that are unsatisfied, or partially unsatisfied, and deferred is \$1.8 million, which the Company expects to recognize through September 2019 as research and development services are performed.

#### *bb21217 license and manufacturing services*

The Company will satisfy its performance obligation related to the manufacture of vectors and associated payload for incorporation into bb21217 through development as the bb21217 manufacturing services are performed. As of December 31, 2018, the manufacturing services for bb21217 had not yet commenced. Therefore, no amounts have been recognized for the combined performance obligation in the consolidate statement of operations for the years ended December 31, 2018, 2017, and 2016.

The aggregate amount of the transaction price allocated to the combined performance obligation, which consists of the bb21217 license and manufacturing services, is \$36.2 million. The Company does not expect that recognition will begin in the next twelve months and has therefore classified deferred revenue associated with the combined performance obligation as deferred revenue, net of current portion on its consolidated balance sheet. The Company had \$9.8 million of remaining deferred revenue as of December 31, 2018 associated with the combined performance obligation consisting of the bb21217 license and manufacturing services.

#### *Contract assets and liabilities - bb2121 and bb21217*

The Company receives payments from its collaborative partners based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until such time as the Company satisfies its performance obligations under these arrangements. A contract asset is a conditional right to consideration in exchange for goods or services that the Company has transferred to a customer. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional.

The following table presents changes in the balances of the Company's Celgene receivables and contract liabilities during the twelve months ended December 31, 2018:

(in thousands)	Balance at beginning of period under Topic 606	Additions	Deductions	Balance at end of period under Topic 606
Receivables	\$ 4,635	\$ 8,570	\$ (6,677 )	\$ 6,528
Contract liabilities:				
Payable included in accrued expenses	\$ -	\$ 8,031	\$ (8,031 )	\$ -
Deferred revenue	\$ 76,812	\$ -	\$ (41,873 )	\$ 34,939

The change in the receivables balance for the year ended December 31, 2018 is primarily driven by cash collected from Celgene for the amounts owed to the Company for the satisfaction of vector manufacturing services performed under the collaboration to date. As of December 31, 2018, the Company has a receivable given that the Company's U.S. development costs incurred in the fourth quarter of 2018 for which Celgene is responsible are in excess of Celgene's U.S. development costs for which the Company is responsible.

The decrease in deferred revenue during the year ended December 31, 2018 is primarily driven by amounts recognized for the combined performance obligation consisting of the bb2121 license and manufacturing services. During the year ended December 31, 2018, \$41.9 million of the deferred revenue balance at the beginning of the period was released from deferred revenue, of which \$32.1 million was recognized as collaboration revenue and \$9.8 million was recorded as contra-research and development expense.

#### **Regeneron**

##### ***Regeneron Collaboration Agreement***

On August 3, 2018, the Company entered into a Collaboration Agreement (the "Regeneron Collaboration Agreement") with Regeneron pursuant to which the parties will apply their respective technology platforms to the discovery, development, and commercialization of novel immune cell therapies for cancer. On August 24, 2018, following the completion of required regulatory reviews, the Regeneron Collaboration Agreement became effective. Under the terms of the agreement, the parties will leverage Regeneron's proprietary platform technologies for the discovery and characterization of fully human antibodies, as well as T cell receptors directed against tumor-specific proteins and peptides and the Company will contribute its field-leading expertise in gene therapy.

In accordance with the Regeneron Collaboration Agreement, the parties jointly selected six initial targets and intend to equally share the costs of research up to the point of submitting an IND application for a potential gene therapy product directed to a particular target. Additional targets may be selected during the five-year research collaboration term as agreed to by the parties.

Regeneron will accrue a certain number of option rights exercisable against targets as the parties reach certain milestones under the terms of the agreement. Upon the acceptance of an IND for the first product candidate directed to a target, Regeneron will have the right to exercise an option for co-development/co-commercialization of product candidates directed to such target on a worldwide or applicable opt-in territory basis, with certain exceptions. Where Regeneron chooses to opt-in, the parties will share equally in the costs of development and commercialization, and will share equally in any profits or losses therefrom in applicable opt-in territories. Outside of the applicable opt-in territories, the target becomes a licensed target and Regeneron would be eligible to receive, with respect to any resulting product, milestone payments of up to \$130.0 million per product and royalties on net sales outside of the applicable opt-in territories at a rate ranging from the mid-single digits to low-double digits. Where Regeneron does not exercise its option, or does not have an option to a target, the target would also become a licensed target.

Either party may terminate a given research program directed to a particular target for convenience, and the other party may elect to continue such research program at its expense, receiving applicable cross-licenses. The terminating party will receive licensed product royalties and milestone payments on the potential applicable gene therapy products. Where the Company terminates a given research program for convenience, and Regeneron elects to continue such research program, the parties will enter into a transitional services agreement. Under certain conditions, following its opt-in, Regeneron may terminate a given collaboration program and the Company may elect to continue the development and commercialization of the applicable potential gene therapy products as licensed products.

#### ***Regeneron Share Purchase Agreement***

A Share Purchase Agreement (“SPA”) was entered into by the parties on August 3, 2018. On August 24, 2018, the closing date of the transaction, the Company issued Regeneron 0.4 million shares of the Company’s common stock, subject to certain restrictions, for \$238.10 per share, or \$100.0 million in the aggregate. The purchase price represents \$63.0 million worth of common stock plus a \$37.0 million premium, which represents a collaboration research advancement, or credit to be applied to Regeneron’s initial 50 percent funding obligation for collaboration research, after which the collaborators will continue to fund ongoing research equally. The collaboration research advancement only applies to pre-IND research activities and is not refundable or creditable against post-IND research activities for any programs where Regeneron exercises their opt-in rights.

#### ***Accounting analysis - Regeneron***

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 0.4 million of the Company’s common shares and joint research activities during the five year research collaboration term. The Company determined the total transaction price to be \$100.0 million, which comprises \$54.5 million attributed to the equity sold to Regeneron and \$45.5 million attributed to the joint research activities. In determining the fair value of the common stock at closing, the Company considered the closing price of the common stock on the closing date of the transaction and included a lack of marketability discount because Regeneron received shares subject to certain restrictions.

The Company analyzed the joint research activities to assess whether they fall within the scope of ASC 808, and will reassess this throughout the life of the arrangement based on changes in the roles and responsibilities of the parties. Based on the terms of the arrangement as outlined above, for the collaboration research performed prior to submission of an IND application for a potential gene therapy product, both parties are deemed to be active participants in the collaboration. Both parties are performing research and development activities and will share equally in these costs through IND. Additionally, Regeneron and the Company are exposed to significant risks and rewards dependent on the commercial success of any product candidates that may result from the collaboration. As such, the collaboration arrangement is deemed to be within the scope of ASC 808.

The \$45.5 million attributed to the joint research activities includes the \$37.0 million creditable against amounts owed to the Company by Regeneron. The collaboration research advancement will be reduced over time for amounts due to the Company by Regeneron as a result of the parties agreeing to share in the costs of collaboration research equally. The remainder of the amount attributed to the joint research activities will be recognized over the five-year research collaboration term.

Consistent with its collaboration accounting policy, the Company will recognize collaboration revenue or research and development expense related to the joint research activities in future periods depending on the amounts incurred by each party in a given reporting period. That is, if the Company’s research costs incurred exceed those research costs incurred by Regeneron in a given quarter, the Company will record collaboration revenue and reduce the original \$37.0 million advance by the amount due from Regeneron until such advancement is fully utilized, after which the Company would record an amount due from Regeneron. If Regeneron’s research costs incurred exceed those research costs incurred by the Company in a given quarter, the Company will record research and development expense and record a liability for the amount due to Regeneron.

The Company recognized approximately \$1.6 million of collaboration revenue under the Regeneron Collaboration Agreement during the year ended December 31, 2018. The Regeneron Collaboration Agreement was entered into in 2018 and as such there was no revenue recognized in 2017 or 2016.

The Company had \$44.0 million remaining collaboration research advancement as of December 31, 2018, \$10.6 million of which is classified as short term.

## **11. License and Royalty Revenue**

### **Novartis Pharma AG**

On April 26, 2017, the Company entered into a worldwide license agreement with Novartis. Under the terms of the agreement, Novartis non-exclusively licensed certain patent rights related to lentiviral vector technology to develop and commercialize CAR T cell therapies for oncology, including Kymriah (formerly known as CTL019), Novartis's anti-CD19 CAR T therapy. At contract inception, financial terms of the agreement included a \$7.5 million payment upon execution, \$7.5 million of potential future milestone payments associated with regulatory approvals, and \$1.1 million of payments for each subsequently licensed product, as well as low single digit royalty payments on net sales of covered products. In August 2017, Novartis received FDA approval for Kymriah and paid the Company \$2.5 million as a result of the achievement of a related milestone.

Given this arrangement is within the scope of Topic 606, the Company assessed this arrangement in accordance with Topic 606 upon transition. The Company identified only one performance obligation, consisting of the license, which was satisfied at contract inception. Accordingly, the nonrefundable license fee of \$7.5 million was recognized as revenue upon contract execution in the second quarter of 2017 and a \$2.5 million regulatory milestone was recognized as revenue upon milestone achievement, also in the second quarter of 2017, given there were no other unsatisfied performance obligations in the arrangement. This accounting conclusion was unchanged from its historical treatment under ASC 605. Regulatory approvals are not within the Company's control or the licensee's control and are generally not considered probable of being achieved until those approvals are received. As such, these milestones are constrained until such time as regulatory approvals are received. Because the single performance obligation was previously satisfied, all regulatory milestones will be recognized as revenue in full in the period in which the associated milestone is achieved.

The Company began recognizing royalty revenue from sales of Kymriah in the fourth quarter of 2017. As the license was deemed to be the predominant item to which the royalties relate, the Company recognizes royalties from the sales of Kymriah when the related sales occur. For the year ended December 31, 2018, the Company recognized royalty revenue of \$2.2 million. During the year ended December 31, 2017, the Company recognized license revenue of \$10.0 million in connection with this arrangement, as there were no other undelivered elements in the arrangement. The Company also recognized \$0.1 million of royalty revenue in connection with this arrangement.

The associated cost of license and royalty revenue for the year ended December 31, 2018 was \$0.9 million. For the year ended December 31, 2017, the cost of license and royalty revenue was \$1.4 million.

As noted in Note 2, "*Summary of significant accounting policies and basis of presentation*," the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed pertaining to prior periods are presented under previous accounting guidance.

### **Orchard Therapeutics Limited (assigned by GlaxoSmithKline Intellectual Property Development Limited)**

On April 28, 2017, the Company entered into a worldwide license agreement with GlaxoSmithKline Intellectual Property Development Limited ("GSK"). Under the terms of the agreement, GSK non-exclusively licensed certain patent rights related to lentiviral vector technology to develop and commercialize gene therapies for Wiscott-Aldrich syndrome and metachromatic leukodystrophy, two rare genetic diseases. Financial terms of the agreement include a nonrefundable upfront payment of \$3.0 million as well as \$1.3 million of potential milestone payments for each marketing authorization for each indication in any country as well as low single digit royalties on net sales of covered products. This license agreement was assigned by GSK to Orchard Therapeutics Limited, effective as of April 11, 2018.

Given this arrangement is within the scope of Topic 606, the Company assessed this arrangement in accordance with Topic 606 upon transition and concluded that at the date of contract inception, only one performance obligation, consisting of the license which was satisfied at contract inception, was identified. Accordingly, the entire nonrefundable license fee of \$3.0 million was recognized as revenue upon contract execution in the second quarter of 2017 given there were no other unsatisfied performance obligations in the arrangement. This accounting conclusion was unchanged from its historical treatment under ASC 605. Regulatory approvals are not within the Company's control or the licensee's control and are generally not considered probable of being achieved until those approvals are received. As such, these milestones are constrained until such time as regulatory approvals are received. During the year ended December 31, 2017, the Company recognized revenue of \$3.0 million upon delivery of the license, as there were no other undelivered elements in the arrangements. There was no revenue recognized under this arrangement in the year ended December 31, 2018. Because the single performance obligation was previously satisfied, all regulatory milestones will be recognized as revenue in full in the period in which the associated milestone is achieved.

For the year ended December 31, 2017 the cost of license and royalty revenue was \$0.1 million. Given there was no revenue recognized under this arrangement in the year ended December 31, 2018, there was no associated cost of license and royalty revenue.

As noted in Note 2, "*Summary of significant accounting policies and basis of presentation*," the Company adopted Topic 606 effective January 1, 2018 using the modified retrospective transition method. Therefore, amounts disclosed pertaining to prior periods are presented under previous accounting guidance.

## **12. Intangible assets**

The Company's intangible assets consist entirely of developed technology, obtained through its acquisition of Pregenex, a privately-held biotechnology company. As a result, the Company obtained gene editing and cell signaling technology with a broad range of potential therapeutic applications. The Company considered the intangible asset acquired to be developed technology, as at the date of the acquisition it could be used the way it was intended to be used in certain ongoing research and development activities. The gene editing platform intangible asset is being amortized to research and development expense over its expected useful life of approximately eight years from the date of the acquisition.

Amortization expense for the gene editing platform intangible asset was \$3.8 million for each of the years ended December 31, 2018, 2017 and 2016, respectively, and accumulated amortization as of December 31, 2018 and 2017 was \$16.9 million and \$13.2 million, respectively. The intangible asset will continue to be amortized on a straight-line basis over its remaining useful life of 3.5 years.

## **13. Stock-based compensation**

On June 3, 2013, the Company's board of directors adopted its 2013 Stock Option and Incentive Plan ("2013 Plan"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO on June 24, 2013. The 2013 Plan replaces the 2010 Stock Option and Grant Plan ("2010 Plan").

The 2013 Plan allows for the granting of incentive stock options, non-qualified stock options, restricted stock units and restricted stock awards to the Company's employees, members of the board of directors, and consultants of the Company. The Company initially reserved 955,000 shares of its common stock for the issuance of awards under the 2013 Plan. The 2013 Plan provides that the number of shares reserved and available for issuance under the 2013 Plan will automatically increase each January 1, beginning on January 1, 2014, by four percent of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Company's compensation committee. In January 2018 and January 2019, the number of common stock available for issuance under the 2013 Plan was increased by approximately 2.0 million and 2.2 million shares, respectively, as a result of this automatic increase provision.

Any options or awards outstanding under the Company's previous stock option plans, including both the 2010 Plan and the Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan ("2002 Plan"), at the time of adoption of the 2013 Plan remain outstanding and effective. The shares of common stock underlying any awards that are forfeited, canceled, repurchased, expire or are otherwise terminated (other than by exercise) under the 2002 Plan and 2010 Plan are added to the shares of common stock available for issuance under the 2013 Plan. As of December 31, 2018, the total number of common stock that may be issued under all plans is 1.5 million.

The Company does not currently hold any treasury shares. Upon stock option exercise, the Company issues new shares and delivers them to the participant.

### **Stock-based compensation expense**

The Company recognized stock-based compensation expense totaling \$110.8 million, \$53.3 million, and \$39.8 million during the years ended December 31, 2018, 2017 and 2016, respectively. Stock-based compensation expense recognized by award type is as follows (in thousands):

	<b>Year ended December 31,</b>		
	<b>2018</b>	<b>2017</b>	<b>2016</b>
Stock options	\$ 83,449	\$ 42,262	\$ 33,966
Restricted stock units	26,628	10,495	5,374
Employee stock purchase plan	759	525	416
	<b>\$ 110,836</b>	<b>\$ 53,282</b>	<b>\$ 39,756</b>

Stock-based compensation expense by classification included within the consolidated statements of operations and comprehensive loss was as follows (in thousands):

	<b>Year ended December 31,</b>		
	<b>2018</b>	<b>2017</b>	<b>2016</b>
Research and development	\$ 54,422	\$ 26,633	\$ 19,690
General and administrative	56,414	26,649	20,066
	<b>\$ 110,836</b>	<b>\$ 53,282</b>	<b>\$ 39,756</b>

In February 2018, the Company issued restricted stock units with service and performance conditions to employees, approximately 0.2 million of which are outstanding as of December 31, 2018 and none of which vested during the year ended December 31, 2018. Vesting of these awards is contingent on the occurrence of a certain regulatory milestone event and fulfillment of any remaining service condition. As a result, the related compensation cost will be first recognized as expense if and when achievement of the regulatory milestone is considered probable. These awards were modified in the second quarter of 2018 as a result of the adoption of a broad-based employee plan. The Company did not recognize any expense during the year ended December 31, 2018 related to these awards and may recognize up to \$37.9 million in stock-based compensation expense related to these awards upon achievement of the performance condition and subject to the service based condition.

As of December 31, 2018, there was \$199.8 million, \$76.4 million and \$0.1 million of unrecognized compensation expense related to unvested stock options, restricted stock units, exclusive of those with service and performance conditions described above, and the employee stock purchase plan, respectively, that is expected to be recognized over a weighted-average period of 2.8, 2.9, and 0.1 years.

### **Stock options**

The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	<b>Year ended December 31,</b>		
	<b>2018</b>	<b>2017</b>	<b>2016</b>
Expected volatility	75.5 %	78.1 %	74.3 %
Expected term (in years)	6.0	6.0	6.0
Risk-free interest rate	2.7 %	2.1 %	1.5 %
Expected dividend yield	0.0 %	0.0 %	0.0 %

The following table summarizes the stock option activity under the Company's equity awards plans:

	Shares (in thousands)	Weighted- average exercise price per share	Weighted- average contractual life (in years)	Aggregate intrinsic value (a) (in thousands)
Outstanding at December 31, 2017	3,755	\$ 67.91		
Granted	1,602	\$ 185.45		
Exercised	(575 )	\$ 51.82		
Canceled or forfeited	(139 )	\$ 130.93		
Outstanding at December 31, 2018	<u>4,643</u>	<u>\$ 108.56</u>	7.5	\$ 110,812
Exercisable at December 31, 2018	<u>2,200</u>	<u>\$ 64.80</u>	6.1	\$ 90,785
Vested and expected to vest at December 31, 2018	<u>4,641</u>	<u>\$ 108.53</u>	7.5	\$ 110,593

(a) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of the common stock for the options that were in the money at December 31, 2018.

The weighted-average fair values of options granted during 2018, 2017 and 2016 was \$125.12, \$62.03, and \$34.22, respectively. The intrinsic value of options exercised during the years ended December 31, 2018, 2017, and 2016, was \$73.1 million, \$91.0 million and \$15.3 million, respectively.

#### **Restricted stock units**

The following table summarizes the restricted stock unit activity under the Company's equity award plans (shares in thousands):

	Shares	Weighted-average grant date fair value
Unvested balance at December 31, 2017	477	\$ 80.72
Granted	673	192.90
Vested	(152 )	86.60
Forfeited	(67 )	149.02
Unvested balance at December 31, 2018	<u>931</u>	<u>\$ 155.99</u>

The intrinsic value of restricted stock units vested during the years ended December 31, 2018, 2017, and 2016 was \$25.5 million, \$8.1 million and \$5.3 million, respectively.

#### **Employee Stock Purchase Plan**

On June 3, 2013, the Company's board of directors adopted its 2013 Employee Stock Purchase Plan ("2013 ESPP"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO on June 24, 2013. The 2013 ESPP authorizes the initial issuance of up to a total of 0.2 million shares of the Company's common stock to participating employees. During the years ended December 31, 2018 and 2017, 16,026 and 20,773 shares of common stock were issued under the 2013 ESPP, respectively.

#### **14. 401(k) Savings plan**

In 1997, the Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code ("the 401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. In March 2019, the Company expects to make contributions of approximately \$2.4 million related to employee contributions made during 2018. In March 2018, the Company made \$1.5 million of contributions related to employee contributions made during 2017. The match contribution is included in accrued expenses and other current liabilities as of December 31, 2018 and 2017. Expense related to the 401(k) Plan totaled \$2.4 million, \$1.5 million, \$1.0 million for the years ended December 31, 2018, 2017, and 2016, respectively.

## 15. Income taxes

The components of loss before income taxes were as follows (in thousands):

	Year ended December 31,		
	2018	2017	2016
U.S.	\$ (440,473 )	\$ (266,236 )	\$ (210,188 )
Foreign	(114,965 )	(69,197 )	(53,931 )
<b>Total</b>	<b>\$ (555,438 )</b>	<b>\$ (335,433 )</b>	<b>\$ (264,119 )</b>

The provision for (benefit from) income taxes were as follows (in thousands):

	Year ended December 31,		
	2018	2017	2016
<b>Current:</b>			
Federal	\$ -	\$ -	\$ -
State	324	115	-
Foreign	222	95	-
<b>Deferred:</b>			
Federal	(307 )	-	(588 )
State	(52 )	-	(24 )
Foreign	-	-	-
<b>Total income tax expense (benefit)</b>	<b>\$ 187</b>	<b>\$ 210</b>	<b>\$ (612 )</b>

A reconciliation of income tax provision (benefit) computed at the statutory federal income tax rate to the Company's effective income tax rate (provision) benefit as reflected in the financial statements is as follows:

	Year ended December 31,		
	2018	2017	2016
Federal income tax expense at statutory rate	21.0 %	34.0 %	34.0 %
State income tax, net of federal benefit	5.1 %	4.3 %	3.3 %
Permanent differences	0.9 %	2.7 %	(5.3 %)
Research and development credit	6.5 %	12.8 %	15.0 %
Foreign differential	(4.4 %)	(6.9 %)	(7.0 %)
Federal tax rate change	0.1 %	(31.6 %)	0.0 %
Other	(0.1 %)	(0.8 %)	0.0 %
Change in valuation allowance	(29.1 %)	(14.6 %)	(39.9 %)
<b>Effective income tax rate (expense) benefit</b>	<b>0.0 %</b>	<b>(0.1 %)</b>	<b>0.1 %</b>

For the years ended December 31, 2018, 2017 and 2016, the Company recognized an income tax (expense) benefit of \$(0.2) million or 0.0%, \$(0.2) million or (0.1%), and \$0.6 million or 0.1%, respectively. The Company did not recognize any significant tax expense for the years ended December 31, 2018, 2017, or 2016 as the Company was subject to a full valuation allowance.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets and liabilities are composed of the following (in thousands):

	<u>Year ended December 31,</u>	
	<u>2018</u>	<u>2017</u>
Deferred tax assets:		
U.S. net operating loss carryforwards (federal and state)	\$ 298,701	\$ 194,160
Tax credit carryforwards (federal and state)	167,517	131,289
Capitalized license fees and research and development expenses	18,083	13,629
60 Binney Street lease	42,059	42,025
Deferred revenue	21,442	12,795
Stock-based compensation	31,858	19,519
Accruals and other	8,886	6,262
Total deferred tax assets	<u>588,546</u>	<u>419,679</u>
Intangible assets	(3,579 )	(4,567 )
Fixed assets	(41,472 )	(42,062 )
Less valuation allowance	(543,495 )	(373,050 )
Net deferred taxes	<u>\$ -</u>	<u>\$ -</u>

A valuation allowance is recorded against deferred tax assets if it is more likely than not that some or all of the deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future tax returns, the Company has recorded a full valuation allowance against the Company's otherwise recognizable net deferred tax assets. The valuation allowance increased on a net basis by approximately \$170.4 million during the year ended December 31, 2018 due primarily to net operating losses, tax credit carryforwards, and stock-based compensation.

As of December 31, 2018, 2017 and 2016, the Company had U.S. federal net operating loss carryforwards of approximately \$1,096.7 million, \$716.1 million, and \$466.8 million, respectively, which may be available to offset future income tax liabilities. Of the amount as of December 31, 2018, \$386.0 million will carryforward indefinitely while \$710.7 million will expire at various dates through 2037. As of December 31, 2018, 2017 and 2016, the Company also had U.S. state net operating loss carryforwards of approximately \$1,082.1 million, \$692.9 million, and \$456.8 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2038. At December 31, 2016, \$195.4 million and \$195.4 million of federal and state net operating losses, respectively, related to excess equity based compensation tax deductions, the benefits for which will be recorded to additional paid-in capital when recognized through a reduction of cash taxes paid. As a result of adopting FASB ASU 2016-09 in the first quarter of 2017, the Company recorded a cumulative-effect adjustment to retained earnings of \$76.7 million to record a net deferred tax asset relative to these tax attribute carryforwards. The deferred tax asset was offset by a corresponding adjustment to the valuation allowance.

As of December 31, 2018, 2017 and 2016, the Company had federal research and development and orphan drug tax credit carryforwards of approximately \$156.2 million, \$124.1 million, and \$83.2 million, respectively, available to reduce future tax liabilities which expire at various dates through 2038. As of December 31, 2018, 2017 and 2016, the Company had state credit carryforwards of approximately \$14.3 million, \$9.1 million, and \$6.0 million, respectively, available to reduce future tax liabilities which expire at various dates through 2033.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception which it believes has resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code.

During the fourth quarter of 2018, the Company completed an analysis of prior year estimates of U.S. research and development and orphan drug tax credits for the years 2013 through 2017. The analysis resulted in an immaterial adjustment to our income tax benefit, which was offset by an adjustment to the valuation allowance.

The Company or one of its subsidiaries files income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2015 through December 31, 2017. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, state or foreign tax authorities to the extent utilized in a future period.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows:

(in thousands)	<u>Unrecognized tax benefits</u>
Balance as of December 31, 2016	\$ -
Increases for tax positions related to current period	-
Increases for tax positions related to prior periods	-
Balance as of December 31, 2017	-
Increases for tax positions related to current period	3,370
Increases for tax positions related to prior periods	8,725
Balance as of December 31, 2018	<u>12,095</u>

The unrecognized tax benefits at December 31, 2018, if recognized, would not affect the Company's effective tax rate due to its full valuation allowance position. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease within the next 12 months. The Company has elected to include interest and penalties related to uncertain tax positions as a component of its provision for income taxes. For the years ended December 31, 2018, 2017 and 2016, the Company's accrued interest and penalties related to uncertain tax positions were not material.

On December 22, 2017, the Tax Cuts and Jobs Act ("TCJA") was enacted. This law substantially amended the Internal Revenue Code and among other things, permanently reduced the U.S. corporate income tax rate from 35% to 21%. On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act ("SAB 118"), which allows the recording of provisional amounts during a measurement period not to extend beyond one year of the enactment date. In accordance with SAB 118, there were no material adjustments recorded and the accounting for these changes has been completed as of December 31, 2018.

#### 16. Net loss per share

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect (in thousands):

	Year ended December 31,		
	2018	2017	2016
Outstanding stock options	4,643	3,755	3,735
Restricted stock units	931	477	263
ESPP shares	10	9	11
	5,584	4,241	4,009

**17. Selected quarterly financial data (unaudited)**

The following table contains quarterly financial information for 2018 and 2017. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2018				
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
(in thousands, except per share data)					
Total revenues	\$ 15,957	\$ 7,851	\$ 11,528	\$ 19,243	\$ 54,579
Total operating expenses	132,586	156,465	161,347	176,204	626,602
Loss from operations	(116,629 )	(148,614 )	(149,819 )	(156,961 )	(572,023 )
Net loss	(115,126 )	(145,996 )	(145,480 )	(149,023 )	(555,625 )
Net loss per share applicable to common stockholders - basic and diluted	\$ (2.31 )	\$ (2.91 )	\$ (2.73 )	\$ (2.72 )	\$ (10.68 )
2017					
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
	(in thousands, except per share data)				
Total revenues	\$ 6,832	\$ 16,716	\$ 7,711	\$ 4,168	\$ 35,427
Total operating expenses	76,745	84,538	85,369	120,940	367,592
Loss from operations	(69,913 )	(67,822 )	(77,658 )	(116,772 )	(332,165 )
Net loss	(68,712 )	(70,898 )	(78,805 )	(117,228 )	(335,643 )
Net loss per share applicable to common stockholders - basic and diluted	\$ (1.68 )	\$ (1.73 )	\$ (1.73 )	\$ (2.52 )	\$ (7.71 )

**Exhibit Index****Incorporated by Reference**

<b>Exhibit Number</b>	<b>Exhibit Title</b>	<b>Form</b>	<b>File no.</b>	<b>Exhibit</b>	<b>Filing Date</b>
2.1	<a href="#"><u>Stock Purchase Agreement by and between the Registrant and Precision Genome Engineering, Inc.</u></a>	8-K	001-35966	2.1	June 30, 2014
3.1	<a href="#"><u>Amended and Restated Certificate of Incorporation of the Registrant</u></a>	8-K	001-35966	3.1	June 24, 2013
3.2	<a href="#"><u>Amended and Restated By-laws of the Registrant</u></a>	8-K	001-35966	3.2	June 24, 2013
3.3	<a href="#"><u>Amendment No. 1 to Amended and Restated By-laws of the Registrant</u></a>	8-K	001-35966	3.1	February 11, 2016
4.1	<a href="#"><u>Specimen Common Stock Certificate</u></a>	S-1/A	333-188605	4.1	June 4, 2013
4.2	<a href="#"><u>Amended and Restated Investors' Rights Agreement, dated as of July 23, 2012, by and among the Registrant and the Investors listed therein.</u></a>	S-1	333-188605	4.5	May 14, 2013
4.3	<a href="#"><u>Amendment to Amended and Restated Investors' Rights Agreement, dated as of July 8, 2014, by and among the Registrant and the Investors listed therein.</u></a>	10-Q	001-35966	4.6	August 12, 2014
10.1#	<a href="#"><u>Second Amended and Restated 2002 Employee, Director and Consultant Plan, as amended, and forms of award agreement thereunder</u></a>	S-1	333-188605	10.1	May 14, 2013
10.2#	<a href="#"><u>2010 Stock Option and Grant Plan, as amended, and forms of award agreement thereunder</u></a>	S-1	333-188605	10.2	May 14, 2013
10.3#	<a href="#"><u>2013 Stock Option and Incentive Plan and forms of award agreement thereunder</u></a>	S-1/A	333-188605	10.3	June 4, 2013
10.4	<a href="#"><u>Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors</u></a>	S-1	333-188605	10.4	May 14, 2013
10.5†	<a href="#"><u>Patent License Agreement, dated December 11, 1996, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc., successor-in-interest to Innogene Pharmaceuticals Inc.) and Massachusetts Institute of Technology, as amended</u></a>	S-1	333-188605	10.6	May 14, 2013
10.6†	<a href="#"><u>Fourth Amendment to Patent License Agreement, dated October 28, 2016, by and between the Registrant and Massachusetts Institute of Technology</u></a>	10-K	001-35966	10.7	February 22, 2017
10.7†	<a href="#"><u>Patent and Know-How License Agreement No. 07554F30, dated May 14, 2009, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc.) and INSERM-TRANSFERT, as amended</u></a>	S-1	333-188605	10.7	May 14, 2013

<u>Incorporated by Reference</u>					
<u>Exhibit Number</u>	<u>Exhibit Title</u>	<u>Form</u>	<u>File no.</u>	<u>Exhibit</u>	<u>Filing Date</u>
10.8†	<a href="#"><u>License Agreement, dated September 13, 2011, by and between the Registrant and Institut Pasteur, as amended</u></a>	S-1	333-188605	10.8	May 14, 2013
10.9†	<a href="#"><u>Amendment No. 3 to License Agreement, dated September 10, 2013, by and between the Registrant and Institut Pasteur</u></a>	10-Q	001-35966	10.2	November 14, 201
10.10†	<a href="#"><u>Amendment No. 4 to License Agreement, dated April 1, 2015, by and between the Registrant and Institut Pasteur</u></a>	10-Q	001-35966	10.10	May 6, 2015
10.11†	<a href="#"><u>License Agreement, dated December 7, 2011, by and between the Registrant and Research Development Foundation</u></a>	S-1	333-188605	10.9	May 14, 2013
10.12†	<a href="#"><u>Novation Agreement, dated April 2, 2012, by and between the Registrant and The Board of Trustees of the Leland Stanford Junior University</u></a>	S-1	333-188605	10.10	May 14, 2013
10.13†	<a href="#"><u>Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated March 19, 2013</u></a>	S-1	333-188605	10.11	May 14, 2013
10.14†	<a href="#"><u>Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated June 3, 2015</u></a>	10-Q	001-35966	10.14	August 7, 2015
10.15	<a href="#"><u>Amendment No. 1 to Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated February 17, 2016</u></a>	10-Q	001-35966	10.15	May 4, 2016
10.16	<a href="#"><u>Amendment No. 2 to Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated September 28, 2017</u></a>	10-Q	001-35966	10.17	November 1, 2017
10.17†	<a href="#"><u>Amended and Restated License Agreement by and between the Registrant and Celgene Corporation, dated February 16, 2016</u></a>	10-Q/A	001-35966	10.16	November 2, 2016
10.18†	<a href="#"><u>Amended and Restated License Agreement by and between the Registrant and Celgene Corporation, dated September 28, 2017</u></a>	10-Q	001-35966	10.19	November 1, 2017
10.19†	<a href="#"><u>Amended and Restated Co-Development, Co-Promote and Profit Share Agreement by and between the Registrant and Celgene Corporation and Celgene European Investment Company LLC, dated March 26, 2018</u></a>	10-Q	001-35966	10.20	May 2, 2018
10.20†	<a href="#"><u>License Agreement by and between the Registrant and Biogen Idec MA Inc., dated August 13, 2014</u></a>	10-Q/A	001-35966	10.17	November 2, 2014
10.21†	<a href="#"><u>Letter Agreement by and between the Registrant and Biogen MA Inc., dated September 29, 2017</u></a>	10-Q	001-35966	10.21	November 1, 2017
10.22†	<a href="#"><u>Exclusive Patent License Agreement by and between the Registrant and the National Institutes of Health, dated August 31, 2015</u></a>	10-Q/A	001-35966	10.18	November 2, 2015

Incorporated by Reference

<u>Exhibit Number</u>	<u>Exhibit Title</u>	<u>Form</u>	<u>File no.</u>	<u>Exhibit</u>	<u>Filing Date</u>
10.23†	<a href="#">License Agreement, dated December 23, 2015, by and between the Registrant and SIRION Biotech GmbH</a>	-	-	-	Filed herewith
10.24†	<a href="#">Toll Manufacturing and Service Agreement, dated November 18, 2016, by and between the Registrant and APCETH Biopharma GmbH</a>	-	-	-	Filed herewith
10.25†	<a href="#">Clinical and Commercial Supply Agreement - Viral Vector Product, dated November 27, 2017, by and between the Registrant and SAFC Carlsbad, Inc.</a>	-	-	-	Filed herewith
10.26#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and Nick Leschly</a>	S-1/A	333-188605	10.12	June 4, 2013
10.27#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and Jeffrey T. Walsh</a>	S-1/A	333-188605	10.13	June 4, 2013
10.28#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and David M. Davidson, M.D.</a>	S-1/A	333-188605	10.15	June 4, 2013
10.29#	<a href="#">Employment Agreement, dated February 3, 2014, by and between the Registrant and Jason F. Cole</a>	10-Q	001-35966	10.18	May 13, 2014
10.30#	<a href="#">Amendment to Employment Agreement, dated March 7, 2016, by and between the Registrant and Jason F. Cole</a>	10-Q	001-35966	10.25	May 4, 2016
10.31#	<a href="#">Amendment No. 2 to Employment Agreement, dated November 3, 2016, by and between the Registrant and Jason F. Cole</a>	10-K	001-35966	10.27	February 22, 2017
10.32#	<a href="#">Employment Agreement, dated May 30, 2015, by and between the Registrant and Philip D. Gregory</a>	10-Q	001-35966	10.21	August 7, 2015
10.33#	<a href="#">Amendment to Employment Agreement, dated November 3, 2016, by and between the Registrant and Philip D. Gregory</a>	10-K	001-35966	10.31	February 22, 2017
10.34#	<a href="#">2013 Employee Stock Purchase Plan</a>	S-1/A	333-188605	10.17	June 4, 2013
10.35#	<a href="#">First Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan</a>	10-K	001-35966	10.38	February 21, 2018
10.36#	<a href="#">Offer Letter, dated November 16, 2017, by and between the Registrant and Kory Wentworth</a>	10-K	001-35966	10.39	February 21, 2018
10.37#	<a href="#">Executive Cash Incentive Bonus Plan</a>	S-1	333-188605	10.18	May 14, 2013
10.38#	<a href="#">Employment Agreement, dated December 18, 2018, by and between the Registrant and William ("Chip") Baird</a>	8-K	001-35966	10.1	February 11, 2019
10.39†	<a href="#">Lease, dated September 21, 2015, by and between the Registrant and ARE-MA Region No. 40 LLC</a>	10-Q	001-35966	10.30	November 5, 2015

<u>Incorporated by Reference</u>				
<u>Exhibit Number</u>	<u>Exhibit Title</u>	<u>Form</u>	<u>File no.</u>	<u>Exhibit</u>
10.40	<a href="#"><u>First Amendment to Lease, dated June 21, 2016, by and between the Registrant and ARE-MA Region No. 40 LLC</u></a>	10-Q	001-35966	10.37
10.41	<a href="#"><u>Second Amendment to Lease, dated November 14, 2016, by and between the Registrant and ARE-MA Region No. 40 LLC</u></a>	10-K	001-35966	10.44
21.1	<a href="#"><u>Subsidiaries of the Registrant</u></a>	-	-	-
23.1	<a href="#"><u>Consent of Ernst &amp; Young LLP</u></a>	-	-	-
31.1	<a href="#"><u>Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</u></a>	-	-	-
31.2	<a href="#"><u>Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</u></a>	-	-	-
32.1	<a href="#"><u>Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.</u></a>	-	-	-
101	The following materials from the Company's Annual Report on Form 10-K for the year ended December 31, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Loss, (iii) Consolidated Statements of Cash Flows and (iv) Notes to Consolidated Financial Statements.	-	-	-

† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been submitted separately to the SEC.

# Indicates a management contract or any compensatory plan, contract or arrangement.

**SIGNATURES**

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

**bluebird bio, Inc.**

By: /s/ Nick Leschly

Nick Leschly

*President, Chief Executive Officer and Director*

**SIGNATURES AND POWER OF ATTORNEY**

We, the undersigned directors and officers of bluebird bio, Inc. (the "Company"), hereby severally constitute and appoint Nick Leschly and Jeffrey Walsh, and each of them singly, our true and lawful attorneys, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this Power of Attorney.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ Nick Leschly	President, Chief Executive Officer and Director <i>(Principal Executive Officer and Duly Authorized Officer)</i>	February 21, 2019
Nick Leschly		
/s/ Jeffrey Walsh	Chief Strategy Officer	February 21, 2019
Jeffrey Walsh		
/s/ Kory Wentworth	Principal Financial Officer and Duly Authorized Officer Vice President, Finance and Treasurer	February 21, 2019
Kory Wentworth		
/s/ Daniel S. Lynch	Principal Accounting Officer Director	February 21, 2019
Daniel S. Lynch		
/s/ John O. Agwunobi, M.D.	Director	February 21, 2019
John O. Agwunobi, M.D.		
/s/ Wendy L. Dixon, Ph.D.	Director	February 21, 2019
Wendy L. Dixon, Ph.D.		
/s/ Mary Lynne Hedley, Ph.D.	Director	February 21, 2019
Mary Lynne Hedley, Ph.D.		
/s/ James Mandell, M.D.	Director	February 21, 2019
James Mandell, M.D.		
/s/ Douglas A. Melton, Ph.D.	Director	February 21, 2019
Douglas A. Melton, Ph.D.		
/s/ David P. Schenkein, M.D.	Director	February 21, 2019
David P. Schenkein, M.D.		
/s/ Mark Vachon	Director	February 21, 2019
Mark Vachon		

# EXHIBIT I

## press release

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### bluebird bio Opens State-of-the-Art Gene and Cell Therapy Manufacturing Facility in Durham, North Carolina

**Gov. Cooper to cut ribbon on facility that will strengthen bluebird bio's capabilities to manufacture products for clinical development and commercial supply**

CAMBRIDGE, Mass. & DURHAM, N.C.--(BUSINESS WIRE)--Mar. 22, 2019-- bluebird bio, Inc. (Nasdaq: BLUE) today announced the official opening of its first wholly owned manufacturing facility in Durham, N.C., that will produce lentiviral vector for the company's investigational gene and cell therapies, including: bb2121 and bb21217 for the treatment of multiple myeloma and potentially LentiGlobin™ for the treatment of transfusion-dependent β-thalassemia (TDT) and sickle cell disease.

Gov. Roy Cooper, Secretary of Commerce Tony Copeland and local patient advocates will join chief bluebird Nick Leschly in a ribbon cutting ceremony at the 125,000-square-foot facility. Currently, bluebird employs approximately 50 scientists, engineers, manufacturing and operations personnel at the facility and is on track to grow to approximately 70 employees by the end of 2019.

"At bluebird bio, we view every aspect of our path to helping patients as both a privilege and a responsibility. This includes the expertise that we've poured into the construction and operation of our manufacturing facility, because it is a crucial step toward our mission of bringing a new generation of treatments to people living with severe genetic diseases and cancer," said Leschly. "Our teams in North Carolina and across the globe are working to deliver treatments that will make a big difference for a lot of patients and families. This is what drives our ambition to bring four gene therapies forward in the next few years."

"North Carolina is proud to bring bluebird bio's cutting-edge work to Durham," Governor Cooper said. "bluebird is developing treatments for devastating diseases that could change the course of medicine. And, with the Triangle's highly-skilled workforce, it will continue to be a leader in the biotech field."

bluebird bio purchased the facility in November 2017. Once completed, the company will have invested more than \$80 million building a world class site equipped with multiple manufacturing suites capable of producing lentiviral vector (LVV). The facility also includes warehouse and quality control testing laboratories. The facility construction is substantially complete and equipment qualification is underway. Initially, bluebird bio expects the facility to produce clinical and commercial supply of lentiviral vector, which is a critical component of the company's gene and cell therapies. The facility is large enough to accommodate significant future expansion, including the possibility of manufacturing commercial drug product.

The goal of gene therapy is to change or replace faulty genes with functional ones in order to prevent, treat or cure a disease. Vectors are selected parts of viruses that have been genetically modified so they can deliver new genes into cells without causing an infectious disease. Prior to gene therapy treatment, copies of functional genes are added to a vector — the delivery system — in a laboratory setting. The vector, with copies of the functional gene, is added to blood stem cells collected from the patient. The cells that now have functional copies of the gene are referred to as gene-modified cells.

In addition to the Durham facility, bluebird bio also has multi-year agreements with three manufacturing partners in the United States and Europe: Brammer Bio (Cambridge, Mass.), Novasep (Gosselies, Belgium) and MilliporeSigma, the Life Science business of Merck KGaA (Carlsbad, Calif.). Each of these partners is collaborating with bluebird bio on production of lentiviral vector across all programs. bluebird bio also partners with Lonza (Houston, Texas) and apceth Biopharma (Munich, Germany) to produce drug product for Lenti-D and LentiGlobin.

bluebird will receive an Economic Development Award from NCBiotech upon meeting job creation targets in North Carolina and will also receive life-sciences-specific employee training support through the North Carolina Community College System's Customized Training Program.

#### About bluebird bio, Inc.

bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene therapies for severe genetic diseases and cancer, with the goal that people facing potentially fatal conditions with limited treatment options can live their lives fully. Beyond our labs, we're working to positively disrupt the healthcare system to create access, transparency and education so that gene therapy can become available to all those who can benefit.

bluebird bio is a human company powered by human stories. We're putting our care and expertise to work across a spectrum of disorders by researching cerebral adrenoleukodystrophy, sickle cell disease, transfusion-dependent β-thalassemia and multiple myeloma using three gene therapy technologies: gene addition, cell therapy and (megaTAL-enabled) gene editing.

bluebird bio has additional nests in Seattle, Wash.; Durham, N.C.; and Zug, Switzerland. For more information, visit [bluebirdbio.com](#).

Follow bluebird bio on social media: [@bluebirdbio](#), [LinkedIn](#), [Instagram](#) and [YouTube](#).

#### Forward-Looking Statements

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the construction and manufacturing capacity of the Company's facility, and the advancement of, and anticipated development and commercialization plans for, the Company's product candidates. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that the Company may not be able to successfully develop, manufacture, market and sell its product candidates, the risk that the Company may not be able to obtain additional funding to support its operations and the risk that the Company may not be able to compete effectively against other companies in the industry.

the timelines we anticipate or at all; the risk that we are unable to successfully operate a manufacturing facility for clinical or commercial

supply; the risks that the preliminary positive efficacy and safety results from our prior and ongoing clinical trials of our product candidates will not continue or be repeated in our ongoing or planned clinical trials; risks that the current or planned clinical trials of our product candidates will be insufficient to support future regulatory submissions or to support marketing approval in the U.S. and EU; and the risk that our product candidates will not be successfully developed, approved or commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent Form 10-K as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

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Source: bluebird bio, Inc.

bluebird bio

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# EXHIBIT J

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, DC 20549**

**FORM 10-K**

**(Mark One)**

**ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2020

OR

**TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to  
Commission File Number: 001-35966

**bluebird bio, Inc.**

**(Exact Name of Registrant as Specified in Its Charter)**

**Delaware**

(State or Other Jurisdiction of  
Incorporation or Organization)

**60 Binney Street**

**Cambridge, Massachusetts**

(Address of Principal Executive Offices)

**13-3680878**

(IRS Employer  
Identification No.)

**02142**

(Zip Code)

**(339) 499-9300**  
(Registrant's Telephone Number, Including Area Code)

**Securities registered pursuant to Section 12(b) of the Act:**

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, \$0.01 par value per share	BLUE	The NASDAQ Stock Market LLC

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. **Yes**  **No**

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. **Yes**  **No**

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. **Yes**  **No**

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). **Yes**  **No**

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant has filed a report on and attested to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). **Yes**  **No**

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 30, 2020, the last business day of the registrant's most recently completed second quarter, was \$4,040,592,242.

As of February 18, 2021, there were 67,141,044 shares of the registrant's common stock, par value \$0.01 per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive Proxy Statement relating to its 2021 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the initiation, timing, progress and results of our preclinical and clinical studies, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical studies;
- our ability to advance our viral vector and drug product manufacturing capabilities, and to ensure adequate supply of our viral vectors and drug products;
- the timing or likelihood of regulatory filings and approvals for our product candidates;
- the timing or success of commercialization of our approved product, and any future approved products;
- our ability to obtain adequate pricing and reimbursement of our approved product, and any future approved products;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our approved product, product candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations and licenses;
- developments relating to our competitors and our industry;
- the impact of the COVID-19 pandemic;
- the timing and results of our investigation into the cause of recent safety events in our HGB-206 clinical study, and whether there is a relationship with the use of our lentiviral vector in the manufacture of LentiGlobin for SCD;
- the timing, effects, costs, and benefits, including the tax treatment of the planned separation of our portfolio of products and programs into two independent, publicly-traded companies; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

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[Table of Contents](#)**Summary of the Material and Other Risks Associated with Our Business**

*Below is a summary of the material risks to our business, operations and the investment in our common stock. This summary does not address all of the risks that we face. Risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K in its entirety before making investment decisions regarding our common stock.*

- The EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary, and we have no assurance as to what the EMA may require, or the timing, if ever, of when ZYNTEGLO may return to the market in Europe.
- The FDA has placed our HGB-206 and HGB-210 clinical studies of LentiGlobin for SCD on clinical hold, and we have no assurance as to what the FDA may require, or the timing, if ever, of when the clinical hold may be lifted.
- We have limited experience as a commercial company and the marketing and sale of ZYNTEGLO or future products may be unsuccessful or less successful than anticipated.
- The commercial success of ZYNTEGLO, and of any future products, will depend upon the degree of market acceptance by physicians, patients, third-party payers and others in the medical community. If we fail to obtain sufficient pricing or reimbursement approval for ZYNTEGLO or any future products, our revenues may be adversely affected and our business may suffer.
- If the market opportunities for our product or any future products are smaller than we believe they are, and if we are not able to successfully identify patients and achieve significant market share, our revenues may be adversely affected and our business may suffer.
- We rely on a complex supply chain for ZYNTEGLO and our product candidates. The manufacture and delivery of our lentiviral vector and drug products present significant challenges for us, and we may not be able to produce our vector and drug products at the quality, quantities, locations or timing needed to support commercialization and clinical programs. In addition, we may encounter challenges with engaging or coordinating with qualified treatment centers needed to support commercialization.
- We cannot predict when or if we will obtain marketing approval to commercialize our product candidates, and the marketing approval of our product and any future products may ultimately be for more narrow indications than we expect.
- We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product and any future products. If our competitors obtain orphan drug exclusivity for products that regulatory authorities determine constitute the same drug and treat the same indications as our product or any future products, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.
- We may not be successful in our efforts to identify or discover additional product candidates.
- We are dependent on BMS for the successful development and commercialization of ide-cel and bb21217. If BMS does not devote sufficient resources to the development of ide-cel and bb21217, is unsuccessful in its efforts, or chooses to terminate its agreements with us, our business will be materially harmed.
- We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.
- From time to time, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.
- Our business may be materially and adversely affected by the ongoing COVID-19 pandemic. The COVID-19 pandemic has had, and will likely continue to have, an impact on various aspects of our business and that of third parties on which we rely. The extent to which the COVID-19 pandemic impacts our business will depend in part on future developments, which are uncertain and unpredictable in nature.

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[Table of Contents](#)**PARTI****Item 1. Business****Overview**

We are a biotechnology company committed to researching, developing, and commercializing potentially transformative gene therapies for severe genetic diseases and cancer. We have built an integrated product platform with broad therapeutic potential in a variety of indications based on our lentiviral gene addition platform, gene editing and cancer immunotherapy capabilities. We believe that gene therapy for severe genetic diseases has the potential to change the way patients living with these diseases are treated by addressing the underlying genetic defect that is the cause of their disease, rather than offering treatments that only address their symptoms. Our programs in severe genetic disease include betibeglogene autotemcel (beti-cel; formerly LentiGlobin gene therapy for β-thalassemia); LentiGlobin gene therapy for sickle cell disease, or SCD; and elivaldogene autotemcel (eli-cel; formerly Lenti-D gene therapy for cerebral adrenoleukodystrophy, or CALD). Our programs in oncology are focused on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. Idecabtagene vicleucel, or ide-cel, and bb21217 are CAR-T cell product candidates for the treatment of multiple myeloma and partnered under our collaboration arrangement with Bristol-Myers Squibb, or BMS.

In January 2021, we announced our intent to separate our severe genetic disease and oncology programs into two separate, independent publicly traded companies, bluebird bio, Inc. and a new company, which we refer to as Oncology NewCo in this annual report on Form 10-K. bluebird bio, Inc. intends to retain focus on our severe genetic disease programs and Oncology NewCo is expected to focus on our oncology programs. The transaction is expected to be completed in late 2021 and is anticipated to be tax-free, subject to receipt of a favorable Internal Revenue Service, or IRS, ruling.

In June 2019, we received conditional marketing approval from the European Commission for beti-cel as a treatment for patients 12 years and older with transfusion-dependent β-thalassemia, or TDT, who do not have a  $\beta^0/\beta^0$  genotype, for whom hematopoietic stem cell, or HSC, transplantation is appropriate, but a human leukocyte antigen-matched, or HLA, related HSC donor is not available. We have begun commercializing beti-cel as ZYNTEGLO in the European Union, or EU, however in February 2021 we temporarily suspended marketing of ZYNTEGLO in light of a suspected unexpected serious adverse reaction, or SUSAR, of acute myeloid leukemia, and a SUSAR of myelodysplastic syndrome in our HGB-206 study of LentiGlobin gene therapy for SCD which is manufactured using the same vector as ZYNTEGLO. Additionally, the European Medicines Agency, or EMA, has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary. We are engaged in discussions with the U.S. Food and Drug Administration, or FDA, for regulatory approval of beti-cel in the United States regarding our proposed development plans for beti-cel as a treatment for patients with TDT. Contingent upon successful resolution of the FDA's concerns arising out of the safety events in our SCD program, we currently expect to complete our biologics license application, or BLA, submission for beti-cel in mid-2021 for the treatment of all patients with TDT across all genotypes. We are engaged with the European Medicines Agency, or EMA, in discussions regarding our proposed development plans for ZYNTEGLO in patients with TDT and  $\beta^0/\beta^0$  genotypes and patients with TDT who are less than 12 years of age.

Based on our prior discussions with the FDA, we believe that we may be able to seek accelerated approval for LentiGlobin for SCD in the United States on the basis of clinical data from Group C of our HGB-206 clinical study, with our HGB-210 clinical study providing confirmatory data for full approval. However, in light of a SUSAR of acute myeloid leukemia and a SUSAR of myelodysplastic syndrome in our HGB-206 clinical study reported to us in February 2021, the FDA has placed our clinical studies of LentiGlobin for SCD on clinical hold. We are investigating these events and plan to continue to work closely with the FDA in their review of these events. In addition, we are also engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin for SCD in Europe.

In October 2020, the EMA accepted our Marketing Authorization Application, or MAA, in the EU for eli-cel for the treatment of patients with CALD. Based on our discussions with the FDA, we believe that we may be able to seek approval from the FDA for eli-cel for the treatment of patients with CALD on the basis of our clinical data from our ongoing Starbeam study, safety data from our ongoing ALD-104 study, and the completed ALD-103 observational study. We currently expect to submit the BLA for eli-cel for the treatment of patients with CALD to the FDA in mid-2021.

In collaboration with BMS, we are developing the ide-cel and bb21217 product candidates as treatments for multiple myeloma. We are co-developing and co-promoting ide-cel in the United States with BMS and we have exclusively licensed to BMS the development and commercialization rights for ide-cel outside of the United States. In September 2020, the FDA accepted for Priority Review the BLA submitted by BMS for ide-cel as a treatment for relapsed and refractory multiple myeloma. We have exclusively licensed the development and commercialization rights for the bb21217 product candidate to BMS, with an option for us to elect to co-develop and co-promote bb21217 within the United States. In addition, we are independently pursuing next-generation BCMA-targeting CAR-T approaches for treating multiple myeloma.

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Our other programs in oncology include programs to discover and develop T cell product candidates to treat other hematologic and solid tumor malignancies, including: non-Hodgkin's lymphoma, acute myeloid leukemia, MAGE-A4 positive solid tumors, and Merkel cell carcinoma.

## **Our Platform**

Our platform is based on lentiviral vectors which are used to introduce a functional copy of a gene to the patient's own isolated HSCs, in the case of our programs in severe genetic diseases, or the patient's own isolated white blood cells which include T cells, in the case of our programs in oncology. Allogeneic hematopoietic stem cell transplant, or allogeneic HSCT, is an existing approach of treating a patient using HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations in the treatment of severe genetic diseases, including difficulties in finding appropriate HLA-matched donors and carries the risk of transplant-related rejection, graft-versus-host disease, or GVHD, and death. Our approach is intended to address the significant limitations of allogeneic HSCT while utilizing existing stem cell transplant infrastructure and processes. Also, because our approach has the potential to drive sustained expression of the functional protein encoded by the gene insert after a single administration, we believe the value proposition offered by our product candidates for patients, families, health care providers and payers would be significant.

## **Our Programs in Severe Genetic Disease**

### ***Betibeglogene autotemcel***

We are developing and commercializing beti-cel as a one-time treatment for transfusion-dependent β-thalassemia, a rare genetic disease caused by a mutation in the β-globin gene resulting in the production of defective red blood cells. The disease is characterized by severe anemia, and the ineffective production of red blood cells can lead to a range of multi-systemic complications, including but not limited to splenomegaly, marrow expansion, bone deformities, and iron overload in major organs (as a result of blood transfusions needed to treat the disease). Our approach involves using a lentiviral vector to insert the normal β-globin gene with a single amino acid substitution into the patient's own HSCs *ex vivo*, to enable formation of normal red blood cells, or RBCs, in patients. Beti-cel refers to the TDT patients' own cells that have undergone our *ex vivo* manufacturing process resulting in genetically modified HSCs.

In June 2019, the European Commission granted conditional marketing authorization for beti-cel, marketed as ZYNTEGLO gene therapy, for the treatment of patients 12 years and older with TDT who do not have a  $\beta^0/\beta^0$  genotype, for whom HSCT is appropriate but an HLA-matched related HSC donor is not available. In February 2021, we temporarily suspended marketing of ZYNTEGLO and the EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary. In addition, the FDA has placed a clinical hold on our HGB-207 and HGB-212 clinical studies. Patient dosing is complete in each of these two studies, and there is no plan to enroll or treat additional patients in these studies. No cases of hematologic malignancy have been reported in any patient who has received treatment with beti-cel, however it is manufactured using the same BB305 lentiviral vector used in LentiGlobin gene therapy for SCD.

In the fourth quarter of 2019, we initiated a rolling submission of a BLA in the United States for beti-cel as a treatment of patients with TDT across all ages and all genotypes, which will be based on data from the Northstar study, the Northstar-2 study, and the Northstar-3 study. Contingent upon successful resolution of the FDA's concerns arising out of the safety events in our SCD program, we currently expect to complete our BLA submission for beti-cel in mid-2021. In addition, we believe the data from our Northstar-3 study, together with data from our Northstar study and Northstar-2 study and HGB-205 study, could be sufficient to form the basis for a MAA variation submission in the EU, for the treatment of patients with TDT and  $\beta^0/\beta^0$  genotypes and patients with TDT who are less than 12 years of age.

Beti-cel has been granted Orphan Drug status by the FDA and EMA for β-thalassemia and was granted Fast-Track designation by the FDA for the treatment of β-thalassemia major. The FDA has granted Breakthrough Therapy designation to beti-cel for the treatment of transfusion-dependent patients with β-thalassemia major, and rare pediatric disease designation for the treatment of TDT. We participated in the EMA's Adaptive Pathways program (formerly referred to as Adaptive Licensing), which is part of the EMA's effort to improve timely access for patients to new medicines. In addition, the EMA has granted Priority Medicines (PRIME) eligibility for beti-cel.

We are conducting the following clinical studies to evaluate the efficacy and safety of beti-cel in the treatment of patients with TDT:

- The Northstar-2 study (HGB-207) is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the safety and efficacy of beti-cel to treat patients with TDT and non- $\beta^0/\beta^0$

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genotypes. Twenty-three patients have been enrolled in the study, consisting of 15 adolescent and adult patients between 12 and 50 years of age at enrollment, and eight pediatric patients less than 12 years of age at enrollment. Age at enrollment ranged from four to 34 years old. To be enrolled, patients with TDT and non- $\beta^0/\beta^0$  genotypes must have received at least 100 mL/kg/year of RBCs or at least eight transfusions per year for the past two years. All patients must be eligible for allogeneic HSCT, but without a matched family HSCT donor. The primary endpoint of this study is the proportion of treated patients who achieve transfusion independence, defined as weighted average hemoglobin levels  $\geq 9.0$  g/dL without any RBC transfusions for a continuous period of at least 12 months at any time during the study after treatment. The secondary endpoints of this study are to quantify gene transfer efficiency and expression, and to measure the effects of treatment with beti-cel on transfusion requirements and clinical events. Safety evaluations to be performed during the study include success and kinetics of platelet and neutrophil engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of clonal dominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.

•The Northstar-3 study (HGB-212) is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the efficacy and safety of beti-cel to treat patients with TDT who have either a  $\beta^0/\beta^0$ ,  $\beta^0/IVS-I-110$ , or  $IVS-I-110/IVS-I-110$  genotypes. As of March 3, 2020, 15 patients have been treated, and median age at enrollment was 15 years of age (ranging from four to 33 years). To be eligible, patients must have received at least 100 mL/kg/year of RBCs or at least eight transfusions per year for the past two years. All patients must be clinically stable and eligible to undergo HSCT, as well as having been treated and followed for at least the last two years in a specialized center that maintained detailed medical records, including transfusion history. The primary endpoint of this study is the proportion of treated patients who meet the definition of "transfusion independence." The secondary endpoints of this study are to measure the proportion of patients who meet the definition of "transfusion reduction," which is defined as demonstration of reduction in volume of RBC transfusion requirements (in mL/kg) in the post-treatment time period of months 12 to 24 compared to the average annual transfusion requirement in the 24 months prior to enrollment, to quantify gene transfer efficiency and expression, and to measure the effects of treatment with beti-cel on transfusion requirements post-treatment and clinical events. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.

In June 2020, we presented the following updated clinical data from our Northstar-2 and Northstar-3 studies at the 25th European Hematology Association (EHA) Annual Congress. All data presented at the EHA Annual Congress and summarized below are as of the data cut-off date of March 3, 2020:

•Efficacy results from Northstar-2 study (HGB-207):

◦All 23 patients enrolled in the study had been treated, with a median follow up period of 19.4 months.

◦Of the 19 patients with sufficient follow-up duration to be evaluable for the primary endpoint of transfusion independence, 89 percent of patients (17 out of 19) had achieved transfusion independence, with median weighted average total hemoglobin levels of 11.9 g/dL (ranging from 9.4 to 12.9 g/dL) over a median of 19.4 months of follow-up to date (ranging from 12.3 to 31.4 months). The 17 patients reaching transfusion independence previously required a median of 17.5 transfusions per year (ranging from 11.5 to 37 transfusions per year).

◦Improved iron levels, as measured by serum ferritin and hepcidin levels (proteins involved in iron storage and homeostasis), were observed and trends toward improved iron management were seen. Over half of patients stopped iron chelation therapy, which is needed to reduce excess iron caused by chronic blood transfusions. Seven out of 23 patients began using phlebotomy for iron reduction.

•Efficacy results from Northstar-3 study (HGB-212):

◦Fifteen patients (nine  $\beta^0/\beta^0$ , three  $\beta^0/\beta^{+IVS1-110}$ , three homozygous IVS-I-110 mutation) had been treated, with a median follow up period of 14.4 months (ranging from 1.1 to 24.0 months).

◦Six of eight evaluable patients achieved transfusion independence, with median weighted average total Hb levels of 11.5 g/dL (ranging from 9.5 to 13.5 g/dL), and continued to maintain transfusion independence for a median duration of 13.6 months (ranging from 12.2 to 21.2 months) as of the data cutoff.

◦Eighty-five percent of patients (11 out of 13) with at least seven months of follow-up had not received a transfusion in more than seven months at time of data cutoff. These eleven patients previously required a median of 18.5 transfusions per year (ranging from 11.0 to 39.5 transfusions per year). In these patients, gene therapy-derived HbA<sup>T87Q</sup> supported total Hb levels ranging from 8.8 to 14.0 g/dL at last visit.

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•Safety results from Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies: Non-serious adverse events (AEs) observed during the HGB-207 and HGB-212 trials that were considered related or possibly related to beti-cel were tachycardia, abdominal pain, pain in extremities, leukopenia, neutropenia and thrombocytopenia. One serious adverse event of thrombocytopenia was considered possibly related to beti-cel. In HGB-207, serious events post-infusion in more than two patients included three events of veno-occlusive liver disease and two events of thrombocytopenia. In HGB-212, serious events post-infusion in more than two patients included two events of pyrexia. Additional adverse events observed in clinical studies were consistent with the known side effects of HSC collection and bone marrow ablation with busulfan, including serious adverse events of veno-occlusive disease. In both Phase 3 studies, there have been no deaths, no graft failure, no cases of vector-mediated replication competent lentivirus or clonal dominance, no leukemia and no lymphoma as of the data cut-off date.

In addition, we have conducted the following clinical studies of beti-cel:

•The Northstar study (HGB-204) is a completed, single-dose, open-label, non-randomized, multi-site phase 1/2 clinical study in the United States, Australia and Thailand to evaluate the safety and efficacy of beti-cel in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. This study was completed in February 2018, and patients in this study were enrolled in a long-term follow-up protocol to assess safety and efficacy beyond the Northstar study follow-up period. Eighteen adults and adolescents were treated in the study. To be eligible for enrollment in this study, patients were between 12 and 35 years of age with a diagnosis of TDT and received at least 100 mL/kg/year of RBCs or at least eight transfusions per year in each of the two years preceding enrollment. The patients were also medically eligible for allogeneic HSCT. Efficacy was evaluated primarily by the production of  $\geq 2.0$  g/dL of hemoglobin A containing  $\beta^{A-T87Q}$ -globin for the six-month period between 18 and 24 months post-treatment. Exploratory efficacy endpoints included RBC transfusion requirements per month and per year, post-treatment. Safety evaluations performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Subjects were monitored by regular screening. Each patient remained on study for approximately 24 months from time of consent and then were enrolled in a long-term follow-up protocol that is assessing safety and efficacy beyond the study protocol's follow-up period.

•The HGB-205 study is a completed, single-dose, open-label, non-randomized, phase 1/2 clinical study at a single site in France to examine the safety and efficacy of beti-cel in four patients with TDT and of LentiGlobin for SCD in three patients with SCD. Patients were required to be between five and 35 years of age with a diagnosis of TDT or SCD at the time of enrollment. To be enrolled, patients with TDT must have received at least 100 mL/kg/year of RBCs per year for the past two years. Those with SCD must have failed to achieve clinical benefit from treatment with hydroxyurea and have an additional poor prognostic risk factor (e.g., recurrent vaso-occlusive crises, or VOCs, or acute chest syndrome, or ACS). All patients must have been eligible for allogeneic HSCT, but without a matched sibling allogeneic HSCT donor. The primary objective of our HGB-205 study was to determine the safety, tolerability and success of engraftment of beti-cel/ LentiGlobin for SCD. The secondary objectives of the study were to quantify gene transfer efficiency and expression, and to measure the effects of treatment with beti-cel/ LentiGlobin for SCD on disease-specific biological parameters and clinical events. In the case of patients with TDT and SCD, this meant the volume of RBC transfusions, and for patients with SCD, it also meant the number of VOCs and ACS in each patient, compared with the two-year period prior to treatment. Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of clonal dominance or leukemia/ lymphoma.

As described above, patients participating in and completing the two years of follow up in either of the Phase 1/2 studies (HGB-204 and HGB-205) or the Phase 3 studies (HGB-207 and HGB-212) were invited to enroll in the 13-year long-term follow-up study LTF-303. In December 2020, we presented updated clinical data from LTF-303 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date as of March 3, 2020:

◦Thirty-two patients were enrolled in LTF-303 (22 treated in Phase 1/2 studies, ten treated in Phase 3 studies) with a median post-infusion follow-up of 49.1 months (ranging from 23.3 to 71.8 months). Of the 32 patients enrolled in LTF-303, transfusion independence was achieved in 64 percent of patients (14 out of 22) treated in Phase 1/2 and in 90 percent of patients (nine out of ten) treated in Phase 3. All patients who achieved transfusion independence remained free from transfusions. The median duration of ongoing transfusion independence was 39.4 months (ranging from 19.4 to 69.4 months). Weighted average Hb in patients who achieved transfusion independence in the Phase 1/2 studies was 10.4 g/dL (ranging from 9.4 to 13.3 g/dL) and 12.5 g/dL (ranging from 11.9 to 13.5 g/dL) in patients who achieved transfusion independence in the Phase 3 studies.

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◦ Median gene therapy-derived hemoglobin (HbA<sup>T87Q</sup>) in all patients treated in the Phase 1/2 studies was stable over time: with a median of 6.4 g/dL (ranging from 0.5 to 10.1 g/dL) in 22 patients at Month 24, a median of 6.7 g/dL (ranging from 0.4 to 10.1 g/dL) in 22 patients at Month 36, a median of 6.6 g/dL (ranging from 0.5 to 10.7 g/dL) in 22 patients at Month 48, and a median of 7.1 g/dL (ranging from 2.8 to 11.2 g/dL) in ten patients at Month 60. Median HbA<sup>T87Q</sup> at Month 24 in all ten patients treated in the Phase 3 studies was 9.5 g/dL (ranging from 0.9 to 12.4 g/dL).

◦ Following an initial increase in liver iron concentration (LIC) after infusion, LIC in patients who achieved transfusion independence decreased, particularly in patients with a high iron burden at baseline. Two patients with severe iron burden (LIC >15 mg/g) and the five patients with significant iron burden (LIC ≥7 - 15 mg/g) at baseline had a median reduction of 59% and 38%, respectively, from baseline to Month 48.

◦ Prior to beti-cel infusion, all patients were on iron chelation, which is needed to reduce excess iron caused by chronic blood transfusions. Fifteen of the 23 patients (65%) who achieved transfusion independence following treatment with beti-cel discontinued iron chelation. Seven of the 23 (30%) were able to receive phlebotomy (blood removal), which is a preferred method for iron reduction.

◦ No cases of death, graft-versus-host disease, and replication-competent lentivirus, clonal dominance or leukemia/ lymphoma were observed as of data cut-off. No drug-related adverse events were reported >2 years post-infusion. Serious adverse events during LTF-303 unrelated to beti-cel included gonadotropin insufficiency, ectopic pregnancy, gall bladder wall thickening/polyp, bacteremia, neutropenia and major depression (with one case of each).

#### **LentiGlobin for Sickle Cell Disease**

We are developing LentiGlobin for SCD as a one-time treatment for patients with SCD, a hereditary blood disorder resulting from a mutation in the β-globin gene that causes polymerization of hemoglobin proteins, resulting in abnormal red blood cell function. The disease is characterized by hemolytic anemia, vaso-occlusive events (or VOEs, repeated acute painful episodes of vaso-occlusion due to sickle cell crises, acute chest syndrome, priapism, or chronic organ damage), cumulative damage to multiple organs, infections, stroke, overall poor quality of life and early death in a large subset of patients. As in our approach with beti-cel in TDT, our approach in SCD involves the *ex vivo* insertion of the normal β-globin gene with the T87Q amino acid substitution using a lentiviral vector into the patient's own HSCs to enable formation of normally functioning hemoglobin A and normal RBCs in patients. In LentiGlobin for SCD, T87Q serves as a distinct biomarker used to quantify expression levels of the functional β-globin protein in patients with SCD, while also providing anti-sickling properties. We refer to the cells that have undergone our *ex vivo* manufacturing process resulting in genetically modified HSCs as LentiGlobin for SCD.

Based on our prior discussions with the FDA, we believe that we may be able to seek accelerated approval for LentiGlobin for SCD in the United States on the basis of clinical data from Group C of our HGB-206 clinical study, with our HGB-210 clinical study providing confirmatory data for full approval. However, in light of a SUSAR of acute myeloid leukemia and a SUSAR of myelodysplastic syndrome in our HGB-206 clinical study reported to us in February 2021, the FDA has placed our clinical studies of LentiGlobin for SCD on clinical hold. We are investigating these events and plan to continue to work closely with the FDA in their review of these events. In addition, we are also engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin for SCD in Europe. LentiGlobin for SCD has been granted Orphan Drug status by the FDA and EMA and Fast-Track designation by the FDA for the treatment of certain patients with SCD. The FDA has also granted Regenerative Medicine Advanced Therapy, or RMAT, designation to LentiGlobin for SCD.

We are conducting, or have conducted, the following clinical studies to evaluate the safety and efficacy of LentiGlobin for SCD in the treatment of patients with SCD:

◦ The HGB-206 study is a single-dose, open-label, non-randomized, multi-site phase 1/2 clinical study in the United States to evaluate the safety and efficacy of LentiGlobin for SCD. Approximately fifty adult and adolescent patients are enrolled in the study. Patients must be at least twelve years of age with a diagnosis of sickle cell disease, with β<sup>S</sup>/β<sup>S</sup>, β<sup>S</sup>/β<sup>+</sup> or β<sup>S</sup>/β<sup>0</sup> genotype. The sickle cell disease must be severe, as defined by recurrent severe VOEs, and patients must have failed to achieve clinical benefit from treatment with hydroxyurea. We refer to the 32 patients treated under the amended study protocol utilizing HSCs from peripheral blood after mobilization with plerixafor as patients in "Group C." The primary efficacy endpoint for this study is complete resolution of severe VOEs, between six and 18 months post-treatment, and the secondary efficacy endpoint for this study is globin response based on β<sup>A-T87Q</sup> expression and total hemoglobin. Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any patient; and the characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.

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In December 2020, we presented updated clinical data from our HGB-206 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized below are as of the data cut-off date as of August 20, 2020:

- A total of 32 patients were treated with LentiGlobin for SCD gene therapy in Group C of HGB-206 and had up to 30.9 months of follow-up with a median of 13.0 months (ranging from 1.1 to 30.9 months).
- In the 22 patients with six or more months of follow-up whose hemoglobin fractions were available, median levels of gene therapy-derived anti-sickling hemoglobin, HbA<sup>T87Q</sup>, were maintained with HbA<sup>T87Q</sup> contributing at least 40% of total hemoglobin at Month 6. Total hemoglobin and HbA<sup>T87Q</sup> ranged from 9.6 to 15.1 g/dL and 2.7 to 8.9 g/dL, respectively.
- At Month 6, the production of HbA<sup>T87Q</sup> was associated with a reduction in the proportion of HbS in total hemoglobin; median HbS was 50% and remained less than 60% at all follow-up timepoints. All patients in Group C were able to stop regular blood transfusions by three months post-treatment and remain off transfusions as of the data cut-off.
- Nineteen patients treated in Group C had a history of severe VOEs, defined as at least four severe VOEs in the 24 months prior to informed consent (annualized rate of severe VOE ranging from 2.0 to 10.5 events) and at least six months follow-up after treatment with LentiGlobin for SCD. There have been no reports of severe VOEs in these Group C patients following treatment with LentiGlobin for SCD. In addition, all 19 patients had a complete resolution of VOEs after Month 6.
- The safety data from Group C patients in HGB-206 remain generally consistent with the known side effects of HSC collection and myeloablative single-agent busulfan conditioning, as well as underlying SCD. One non-serious, Grade 2 adverse event (AE) of febrile neutropenia was considered related to LentiGlobin for SCD. There were no serious AEs related to LentiGlobin for SCD. One patient with significant baseline SCD-related and cardiopulmonary disease died 20 months post-treatment; the treating physician and an independent monitoring committee agreed his death was unlikely related to LentiGlobin for SCD and that SCD-related cardiac and pulmonary disease contributed.
- HGB-210 is a single-dose, open-label, non-randomized, multi-site, international phase 3 clinical study to evaluate the efficacy and safety of LentiGlobin for SCD in the treatment of patients with SCD and a history of vaso-occlusive events, or VOEs, with a target enrollment of 35 pediatric, adolescent and adult patients. Patients must be at least two years of age at enrollment with a diagnosis of sickle cell disease, with β<sup>S</sup>/β<sup>S</sup>, β<sup>S</sup>/β<sup>+</sup> or β<sup>S</sup>/β<sup>0</sup> genotype. The sickle cell disease must be severe, as defined by recurrent severe VOEs, and patients must have failed to achieve clinical benefit from treatment with hydroxyurea. The patients must also be eligible for HSCT. The primary efficacy endpoint for this study is globin response based on β<sup>A-T87Q</sup> expression and total hemoglobin, and the secondary efficacy endpoint for this study is 75% reduction in annualized severe VOEs. Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any patient; and the characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the study protocol's follow-up period.
- HGB-205 is a completed single-center phase 1/2 study in France of patients with SCD which also enrolled patients with TDT.

#### *Elivaldogene autotemcel*

We are developing eli-cel as a one-time treatment for CALD, the most severe form of adrenoleukodystrophy, a rare X-linked metabolic disorder caused by mutations in the ABCD1 gene, which results in accumulation of very long-chain fatty acids in plasma and tissues, leading to a range of clinical outcomes. CALD involves a progressive destruction of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of neurological function and eventual death in most patients. Our approach involves the *ex vivo* insertion of a functional copy of the ABCD1 gene via a lentiviral vector into the patient's own HSCs. Following engraftment, we expect the transduced HSCs to differentiate into other cell types, including macrophages and cerebral microglia, which produce functional ALDP. We believe that the functional ALDP can then enable the local degradation of VLCFAs in the brain, which in turn can stabilize the disease by preventing further cerebral inflammation and demyelination that are characteristics of CALD.

In October 2020, the EMA accepted our Marketing Authorization Application in the EU for eli-cel for the treatment of patients with CALD. Based on our discussions with the FDA, we believe that we may be able to seek approval for eli-cel for the treatment of patients with CALD on the basis of safety and efficacy data from our ongoing Starbeam study, safety data from our ongoing ALD-104 study, and the completed ALD-103 observational study. For the assessment of efficacy, we expect that the clinical results of the Starbeam study will be compared to a clinically meaningful benchmark based on the medical literature

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and data collected in ALD-101, a retrospective analysis that assessed the natural history of CALD, as well as outcomes of patients with CALD who had received allogeneic HSCT. For the assessment of safety, we expect that the clinical results of the Starbeam study will be compared to data collected from the ALD-103 study, a multinational, multi-site, prospective and retrospective observational study designed to evaluate outcomes of allogeneic HSCT in patients with CALD. We currently expect to submit the BLA for eli-cel for the treatment of patients with CALD in mid-2021. Eli-cel has been granted Orphan Drug status by the FDA and EMA for adrenoleukodystrophy. The FDA has granted Breakthrough Therapy designation and the EMA has granted PRIME eligibility to eli-cel.

We are conducting the following studies to evaluate the safety and efficacy of eli-cel in the treatment of patients with CALD:

- The Starbeam study (ALD-102) is a single-dose, open-label, non-randomized, international, multi-site phase 2/3 study to evaluate the safety and efficacy of eli-cel in males with CALD  $\leq$  17 years of age. Thirty-two patients have been enrolled in this study. Key inclusion criteria included: male and, at time of enrollment,  $\leq$  17 years of age and with a neurologic function score (NFS) of  $\leq$  1, with active CALD as defined by elevated very long chain fatty acids (VLCFA) levels, and brain magnetic resonance imaging (MRI) demonstrating Loes score between 0.5 and  $\leq$  9 (inclusive) and evidence of gadolinium enhancement (GdE $^{+}$ ). Patients with a willing, unaffected 10/10 HLA-matched sibling HSC donor were excluded from the study. The primary efficacy endpoint of the study is the proportion of patients who are alive and free of six major functional disabilities, or MFD, at 24 months post-treatment. MFDs were defined as loss of communication, complete loss of voluntary movement, cortical blindness, tube feeding, wheelchair dependence, and total incontinence. These six MFDs were selected as they are considered to have the most significant impact on the ability of patients with CALD to function independently, representing unambiguous and profound neurologic degeneration. Secondary and exploratory endpoints included monitoring over time of the following: NFS, a 25-point scale used to evaluate the severity of gross neurologic dysfunction by scoring 15 neurological abnormalities across multiple domains; Loes score, a 34-point scale designed to objectively measure the extent of demyelination and atrophy in CALD patients, based on brain magnetic resonance imaging, or MRI, studies; and gadolinium enhancement status, associated with inflammation and disruption of the blood brain barrier on brain MRI.

The primary safety endpoint is the proportion of patients who experience either  $\geq$  Grade 2 acute GVHD or chronic GVHD by 2 years post-treatment. Some additional safety evaluations include the following: success and kinetics of HSC engraftment, incidence of transplant-related mortality; detection of vector-derived replication-competent lentivirus; and characterization and quantification of events related to the location of insertion of the functional *ABCD1* gene in target cells. Patients will be followed for 24 months post-treatment under this protocol. In accordance with applicable guidance from the FDA and EMA, we will be monitoring patients in a separate long-term follow up protocol (LTF-304) to evaluate safety for up to 15 years, and will also monitor efficacy endpoints to demonstrate a sustained treatment effect.

In August 2020, we presented updated clinical data at the 46th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT). All data presented and summarized below are as of January 2020, except as otherwise indicated:

- The data reflect a total patient population of 32 patients in the study, with a median follow-up time of 30.0 months and a range of 9.1 to 70.7 months. Of the 32 patients who have received eli-cel, 20 had completed ALD-102 and were enrolled in LTF-304, while nine continued to be followed in ALD-102 not having reached 24 months post-treatment, and three were no longer on-study. Of the three patients who are no longer on the study, two withdrew from the study at investigator discretion, and one experienced rapid disease progression early in the study, resulting in MFDs and death.
- Of the 23 patients who have or would have reached 24 months of follow-up and completed the study, 87 percent (20 out of 23) have met the primary endpoint and continue to be alive and MFD-free in LTF-304. Fourteen patients have at least four years of follow-up, including ten patients who have reached at least their Year 5 follow-up visit. The nine patients from ALD-102 that have not reached Month 24 have shown no evidence of MFDs.
- Of the 32 patients who have received eli-cel, 31 had stable NFS (NFS  $\leq$  4, without a change of  $>3$  from baseline) and 24 patients maintained an NFS of 0 following treatment.
- As of the data cut-off date, no acute or chronic GvHD have been reported post-treatment and there have been no reports of graft failure or graft rejection. The treatment regimen, comprising mobilization/apheresis, conditioning, and eli-cel infusion, had a safety and tolerability profile primarily reflective of the known effects of mobilization/apheresis and conditioning. In ALD-102, as previously reported, three adverse events were considered possibly related to eli-cel and include one serious adverse event (Grade 3 BK viral cystitis),

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and two non-serious adverse events (Grade 1 vomiting). All three adverse events resolved using standard measures.

- There have been no cases of replication competent lentivirus or insertional oncogenesis as of the data-cut off date. Integration site analysis was conducted to determine the pattern of proviral integration post-eli-cel treatment and assess whether dominant or expanding clones were present. In one patient, now enrolled in LTF-304 for long-term follow up, a case of benign clonal expansion was observed with three separate integrations in the DNA of the cell at ACER3, RFX3, and MECOM. As of the patient's Month 62 visit in March 2020, the patient remained clinically stable. Bone marrow analyses showed no dysplasia (abnormal cell growth) or molecular abnormalities.

- The ALD-104 study is an open-label, non-randomized, international, multi-site phase 3 study to evaluate the safety and efficacy of eli-cel in males with CALD ≤ 17 years of age after myeloablative conditioning using busulfan and fludarabine, a different chemotherapy conditioning regimen than what is used in ALD-102 (busulfan and cyclophosphamide). Target enrollment in ALD-104 is 35 patients. Key inclusion criteria included: male and, at time of enrollment, ≤ 17 years of age and with a neurologic function score (NFS) of ≤ 1, with active CALD as defined by elevated very long chain fatty acids (VLCFA) levels, and brain magnetic resonance imaging (MRI) demonstrating Loes score between 0.5 and ≤ 9 (inclusive) and evidence of gadolinium enhancement (GdE+). The primary efficacy endpoint of the study is the proportion of patients who are alive and free of six MFDs at 24 months post-treatment. Secondary and exploratory endpoints included monitoring over time of the following: NFS, Loes score, and gadolinium enhancement status, associated with inflammation and disruption of the blood-brain barrier on brain MRI. The primary safety endpoint is the proportion of patients with neutrophil engraftment after eli-cel infusion (time frame: 42 days post drug-product infusion).

In August 2020, we presented updated clinical data at the 46th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT). All data presented and summarized below are as of February 2020:

- 13 patients were on study with a median of 6.1 months of follow-up (ranging from 2.2 to 10.3 months). All 13 patients achieved neutrophil engraftment and 12 out of 13 evaluable patients had platelet engraftment (platelet engraftment pending in one patient as of data cut date).

- No events of acute or chronic GvHD had been reported and there have been no reports of graft failure, graft rejection, cases of insertional oncogenesis, or replication competent lentivirus.

- The treatment regimen, comprising mobilization/apheresis, conditioning, and eli-cel infusion had a safety and tolerability profile primarily reflective of the known effects of mobilization/apheresis and conditioning. Two adverse events of pancytopenia were considered possibly related to eli-cel. These two ongoing adverse events were deemed as suspected unexpected serious adverse reactions by the principal investigator and were diagnosed approximately two months post-eli-cel treatment in two patients (one Grade 2 and one Grade 3). An additional serious adverse event was ongoing as of February 2020, a Grade 3 transverse myelitis that was diagnosed in the presence of viral infection (adenovirus and rhinovirus/enterovirus positivity) approximately six months after eli-cel treatment and deemed unrelated to eli-cel.

- The ALD-103 study is a completed observational prospective/ partially retrospective data collection study of 59 patients with CALD ≤ 17 years of age who received allogeneic HSCT. This study was designed to collect efficacy and safety outcomes data in patients who had undergone allogeneic HSCT in a period that is contemporaneous with the Starbeam study. The study measured CALD disease-related outcomes in four patient cohorts: early disease 1 (N=21; Loes ≤ 4 and NFS ≤ 1); early disease 2 (N=9; Loes > 4 to 9 and NFS ≤ 1); all early disease (N=30; Loes ≤ 9 and NFS ≤ 1); and advanced disease (N=10; Loes > 9 or NFS > 1). Transplant-related outcomes were assessed by donor stem cell source, by donor match, and by conditioning regimen. We anticipate that eli-cel safety and efficacy will be evaluated by the FDA and EMA in light of the data collected in the Starbeam study in conjunction with our retrospective observational ALD-101 study and our retrospective and prospective observational ALD-103 study, as well as safety results from our ongoing ALD-104 study.

#### ***Strategic collaborations in severe genetic disease***

We have formed and intend to seek other opportunities to form strategic collaborations with third parties who can augment our industry-leading gene therapy platform and expertise, and to access the substantial funding and other resources required to develop and commercialize gene therapy products. To date, we have focused on forging a limited number of significant strategic collaborations with leading pharmaceutical companies and academic research centers where both parties contribute expertise to enable the discovery and development of potential product candidates. Currently, our strategic collaborations in severe genetic disease include those with:

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- Magenta Therapeutics, Inc., to evaluate the utility of MGTA-145 in combination with plerixafor for mobilization and collection of stem cells in adults and adolescents with SCD, through a proof-of-concept clinical trial;
- Novo Nordisk A/S, to jointly develop next-generation *in vivo* genome editing treatments for genetic diseases, including hemophilia; and
- Forty Seven, Inc., a subsidiary of Gilead Sciences, Inc., to pursue clinical proof-of-concept for an antibody-based conditioning regimen in combination with our *ex vivo* lentiviral gene therapy platform.

***Manufacturing in severe genetic disease***

We have entered into multi-year agreements with external manufacturing partners in the United States and Europe to support our clinical and commercial programs in severe genetic disease. We have multi-year agreements with SAFC Carlsbad, Inc., or SAFC (a subsidiary of MilliporeSigma), and Thermo Fisher Scientific, Inc. (previously Novasep) in the production of lentiviral vector. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. and Minaris Regenerative Medicine, or Minaris, to produce drug product. Currently to support the commercialization of beti-cel in Europe, SAFC is our sole manufacturer of lentiviral vector, and Minaris is our sole manufacturer of drug product. In our manufacturing agreement with SAFC, we are required to provide rolling forecasts for products on a quarterly basis, a portion of which will be considered a binding, firm order, subject to a purchase commitment. In our manufacturing agreement with Minaris, we reserve production capacity for the manufacture of our drug product. In addition, we rely on specialized third-party testing organizations to confirm the quality of vector and drug product prior to their use in clinical trials and in the commercial context.

We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing activities, and to compile manufacturing and quality information for our regulatory submissions and commercialization efforts. For the treatment of patients with our drug product in the commercial setting, we are partnering with participating apheresis centers, which we refer to as qualified treatment centers, to be centers for collection of HSCs from the patient and for infusion of drug product to the patient.

***Commercial operations***

We are commercializing ZYNTEGLO in the European Union and the United Kingdom, following our receipt of conditional marketing approval by the European Commission in June 2019. In February 2021, we temporarily suspended marketing of ZYNTEGLO and the EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary. As we transition into a commercial-stage company, we have established commercial operations in Europe, and have begun to build commercial operations in the United States, with a goal of delivering our gene therapies, if and once approved, to patients through qualified treatment centers. In the course of preparing to treat our first commercial patients, we have established commercial capabilities across the European Union, and in the United States and United Kingdom by adding employees with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. Our commercialization activities include active engagement with stakeholders across the healthcare system, including those with public and private payers, patient advocates and organizations, professional societies, and healthcare providers, to explore new payment models that we hope will enable access for more patients. Ultimately, we intend to leverage our commercial infrastructure to support the potential for multiple product launches sequentially across multiple geographies. For many territories and countries, we may also elect to utilize strategic collaborators, including distributors, or contract field-based teams to assist in the commercialization of our product and potential future products.

While we have largely established the appropriate quality systems, compliance policies, systems and procedures, as well as internal systems and infrastructure necessary for supporting our complex supply chain and commercialization activities, we expect that we may make additional targeted investments as we continue our efforts in adding sites to our network of qualified treatment centers, establishing patient-focused programs, educating healthcare professionals, and securing reimbursement.

The timing and conduct of our commercialization activities will be dependent upon regulatory interactions, marketing approvals received for our product and potential future products, and on agreements we have made or may make in the future with strategic collaborators.

***Our Programs in Oncology***

We are pursuing multiple programs that leverage the unique properties of lentiviral vectors to target T cells as a therapy for various cancers. This represents a direct application of our expertise in gene therapy and our capabilities, know-how and patents associated with lentiviral gene therapy and gene editing for *ex vivo* applications. Our oncology programs use a customized

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lentiviral vector to alter T cells, rather than HSCs, so that the T cells can recognize specific proteins or protein fragments on the surface of cancer cells in order to kill these diseased cells. T cells that have been genetically-engineered *ex vivo* to make CAR or TCRs are designed to help a patient's immune system overcome survival mechanisms employed by cancer cells. CAR T cell technology directs T cells to recognize cancer cells based on expression of specific cell surface antigens, whereas TCR T cell technology provides the T cells with a specific T cell receptor that recognizes protein fragments derived from either intracellular or extracellular proteins which are displayed on the tumor cell surface. The genetically-engineered T cells are designed to supplement a patient's immune system and may be further engineered to overcome immune evasion mechanisms employed by cancer cells. For instance, we are exploring applications of our CAR and TCR T cell technologies in combination with novel proteins based on synthetic biology. These technologies may potentially allow our future T cell-based product candidates to detect the tumor microenvironment or to be regulated by small molecules. In addition, using our gene editing technology, we potentially have a number of additional options to manipulate the genome of the cancer patient's T cells to further increase the specificity of the anti-tumor activity and to potentially make these cells even more potent. All of the gene-editing technologies currently being explored by the pharmaceutical industry, including zinc finger nucleases, CRISPR/Cas9, and TALENs, share common features of a DNA binding domain and a DNA cleavage domain. They differ in specificity, size, ease of delivery and as naturally occurring versus engineered nucleases. Our gene editing platform is based on homing endonucleases and megaTALs, based on a naturally-occurring class of DNA cleaving enzymes that function as monomeric proteins able to bind DNA in a sequence-specific manner and cleave their target site. We believe there are multiple advantages of homing endonucleases and megaTALs compared to other gene editing technologies, most notably: they are highly specific and efficient in cutting DNA and their compact size simplifies delivery to therapeutically relevant cell types. We are using our gene editing platform, along with collaborations with multiple academic institutions, to potentially discover and develop next-generation gene therapy and oncology product candidates.

Our programs in oncology include ide-cel and bb21217 in multiple myeloma, which we are developing in collaboration with BMS, and preclinical programs to discover and develop T cell product candidates to treat other hematologic and solid tumor malignancies, including: non-Hodgkin's lymphoma, acute myeloid leukemia (in collaboration with Seattle Children's Research Institute), MAGE-A4 positive solid tumors (in collaboration with Regeneron), and Merkel cell carcinoma (in collaboration with Fred Hutchinson Cancer Research Center). We are also independently researching and developing other CAR T cell product candidates against a variety of cancer targets, including next-generation anti-BCMA CAR-T cell products for the treatment of multiple myeloma.

#### *Ide-cel and bb21217*

In collaboration with BMS, we are developing ide-cel and bb21217, with the goal of filing for regulatory approval for the treatment of multiple myeloma on a global basis. Ide-cel and bb21217 both bind to BCMA, a cell surface protein expressed on normal plasma cells, some mature B cells, and on malignant multiple myeloma cells, but not on other cells. Ide-cel and bb21217 arose from our multi-year collaboration with Celgene Corporation, or Celgene, which was acquired by BMS in November 2019. We co-develop and co-commercialize ide-cel in the United States with BMS, in which we share equally in costs and any profits. BMS has the exclusive license to develop and commercialize ide-cel outside of the United States. BMS has the exclusive worldwide license to develop and commercialize bb21217, and we retain an option to co-develop and co-commercialize this product candidate in the United States. The terms of our arrangements with BMS are described more fully below under "*Strategic collaborations in oncology-Our strategic alliance with BMS*."

In September 2020, the FDA accepted for Priority Review the BLA submitted by BMS for ide-cel as a treatment for relapsed and refractory multiple myeloma. The FDA and EMA have granted Orphan Drug status to both ide-cel and bb21217 for the treatment of patients with relapsed and refractory multiple myeloma. The FDA has granted Breakthrough Therapy designation and the EMA has granted PRIME eligibility to ide-cel for relapsed and refractory multiple myeloma.

For the development of ide-cel, BMS is conducting, or is planning to conduct, the following clinical studies in multiple myeloma:

- The KarMMa study, a pivotal open-label, single arm, multicenter, phase 2 study evaluating the safety and efficacy of ide-cel in adult patients with relapsed and refractory multiple myeloma in North America and Europe. All enrolled patients had received at least three prior regimens, including an immunomodulatory (IMiD) agent, a proteasome inhibitor (PI) and an anti-CD38 antibody, and all were refractory to their last regimen, defined as progression during or within 60 days of their last therapy. Ninety-four percent of patients were refractory to an anti-CD38 antibody and 84% percent were triple refractory (refractory to an IMiD agent, PI and anti-CD38 antibody).

The primary endpoint of the study is overall response rate (ORR) as assessed by an independent review committee (IRC) according to the International Myeloma Working Group (IMWG) criteria. Complete response rate (CR) is the key secondary endpoint. Other efficacy endpoints include time to response, duration of response (DoR), progression-free survival (PFS), overall survival and minimal residual disease (MRD) evaluated by next-generation sequencing assay. The study enrolled 140 patients, of whom 128 patients were treated with ide-cel across the target dose levels of

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$150-450 \times 10^6$  CAR+ T cells after receiving lymphodepleting chemotherapy. In May 2020, we and BMS presented the results at the American Society of Clinical Oncology 2020 Virtual Scientific Program, as summarized below:

◦ 128 patients were treated with ide-cel across target dose levels of  $150$  to  $450 \times 10^6$  CAR+ T cells. Patients had a median of six prior regimens; 84% were refractory to all three classes of commonly used treatments including an IMiD, a PI and an anti-CD38 antibody, and 94% were refractory to anti-CD38 antibodies. Median duration of follow-up was 13.3 months.

◦ Results for the primary endpoint (ORR) and key secondary endpoint (CR), as well as median duration of response (DoR) and median progression-free survival (PFS) across the target dose levels and at each of the three target doses explored in the study were as follows:

CAR+ T cell dose level	$150 \times 10^6$	$300 \times 10^6$	$450 \times 10^6$	$150-450 \times 10^6$
N	4	70	54	128
<b>Measures:</b>				
Overall response rate, n (%)	2 (50)	48 (69)	44 (82)	94 (73)
Complete response (CR)/ Stringent CR, n (%)	1 (25)	20 (29)	21 (39)	42 (33)
Median DoR, months	†	9.9	11.3	10.7
Median DoR by best response (CR/sCR), months	†	††	††	19.0
Median PFS, months	2.8	5.8	12.1	8.8
Median PFS by best response (CR/sCR), months	†	††	††	20.2
†Not reported due to small n				
††Data not reported				

◦ The overall response rate (ORR) was 73% across all dose levels, including 33% of patients who had a complete response (CR) or stringent CR (sCR). Median duration of response (DoR) was 10.7 months, with 19.0 month median DoR for patients who had a CR or sCR. Median progression-free survival (PFS) was 8.8 months, with 20.2 month median PFS for patients who had a CR or sCR. All patients who had CR or sCR and were evaluable for minimal residual disease (MRD), were MRD-negative. Clinically meaningful benefit was consistently observed across subgroups, and nearly all subgroups had an ORR of 50% or greater, including older and high-risk patients. The overall survival (OS) data continue to mature, with an estimated median OS of 19.4 months across all dose levels and 78% of patients alive at 12 months. Results support a favorable benefit-risk profile for ide-cel across the target dose levels of  $150$  to  $450 \times 10^6$  CAR+ T cells.

◦ The most frequently reported adverse events were cytopenia and cytokine release syndrome (CRS). Cytopenias were common and not dose related. Overall, CRS of any grade was reported in 84% (107/128) of patients. Grade 3 or higher CRS occurred in <6% (7/128) of patients, with one fatal CRS event. Investigator identified neurotoxicity events (iiNT) were reported in 18% (23/128) of patients, including Grade 3 iiNT reported in 3% (4/128) of patients. There were no Grade 4 or Grade 5 iiNT events reported.

• The CRB-401 study, a single-dose, open-label, non-randomized, multi-site phase 1 dose escalation/ dose expansion clinical study in the United States to examine the safety and efficacy of ide-cel in up to 67 patients with relapsed and refractory multiple myeloma. In order to be eligible for CRB-401, patients must have received three prior regimens, including a proteasome inhibitor (PI; bortezomib or carfilzomib) and an immunomodulatory agent (IMiD; lenalidomide or pomalidomide), or be “double-refractory” to both a proteasome inhibitor and an immunomodulatory agent. In the expansion cohort, patients must have received at least a PI, an IMiD and daratumumab, and be refractory to their last line of therapy. Patients receive one cycle of lymphodepletion with cyclophosphamide and fludarabine prior to infusion of the bb2121 drug product.

The primary endpoint of the study is the incidence of adverse events and abnormal laboratory test results, including dose-limiting toxicities. The study also seeks to assess disease-specific response including: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. The study also seeks to determine the maximally tolerated dose and recommended dose for further clinical trials. Each patient is followed for up to 60 months post-treatment, and then is enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 60-month period.

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In December 2020, we presented updated results from the CRB-401 study at the ASH Annual Meeting as summarized below:

• 62 patients were treated with ide-cel across dose levels of 50, 150, 450, or  $800 \times 10^6$  CAR positive T cells. Among the 62 patients treated with ide-cel in this study, the overall response rate (ORR) was 76%, including 24 patients (39%) who achieved a complete response (CR). The median duration of response (DoR) was 10.3 months. Median PFS was 8.8 months and median OS was 34.2 months, with a median follow-up of 14.7 months.

• Safety remained consistent with previously reported results from CRB-401. Among all infused patients, the most frequent adverse events were neutropenia (92%), cytokine release syndrome (CRS; 76%), anemia (76%), and thrombocytopenia (74%). The most frequent Grade 3/4 adverse events were neutropenia (89%), leukopenia (61%), anemia (57%), and thrombocytopenia (57%). Most CRS events were Grade 1 or 2. Four patients (7%) had Grade 3 CRS; there were no Grade 4 or 5 CRS events reported.

• the KarMMA-2 study, an open-label, multi-cohort, multi-center phase 2 study of patients with relapsed and refractory multiple myeloma and in high-risk multiple myeloma.

• the KarMMA-3 study, an open-label, randomized, multi-center, phase 3 study comparing the efficacy and safety of ide-cel versus standard triplet regimens in patients with relapsed and refractory multiple myeloma.

• the KarMMA-4 study, an open label, single-arm, multi-center, phase 1 study intended to determine the optimal target dose and safety of ide-cel in patients with high-risk newly-diagnosed multiple myeloma.

For the development of the bb21217 product candidate, we are conducting the CRB-402 study, a single-dose, open label, single-arm, multi-center, phase 1 dose escalation/ dose expansion clinical study in the United States to examine the safety and efficacy of our bb21217 product candidate in up to 74 patients with relapsed and refractory multiple myeloma. In order to be eligible for CRB-402, patients must have received three prior regimens, including a proteasome inhibitor (PI: bortezomib or carfilzomib) and immunomodulatory agent (IMiD: lenalidomide or pomalidomide), or be “double-refractory” to both a proteasome inhibitor and an immunomodulatory agent. In the expansion cohort, patients must have received at least a PI, and IMiD and daratumumab, and be refractory to their last line of therapy. Patients receive one cycle of lymphodepletion with cyclophosphamide and fludarabine prior to infusion of the bb21217 drug product.

The primary endpoint of the study is the incidence of adverse events and abnormal laboratory test results, including dose-limiting toxicities. The study also seeks to assess disease-specific response including: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. The study also seeks to determine the maximally tolerated dose and recommended dose for further clinical trials. Each patient will be followed for up to 60 months post-treatment, and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond the 60-month period.

In December 2020, we presented updated clinical data from the CRB-402 study at the ASH Annual Meeting. All data presented at the ASH Annual Meeting and summarized here are as of the data cut-off date of September 1, 2020. Sixty-nine patients received treatment as of the data cut-off. Patients had a median of six prior lines of therapy and 78 percent of patients received at least one prior autologous stem cell transplant.

CAR+ T cell dose level	$150 \times 10^6$ (n=12)	$300 \times 10^6$ (n=14)	$450 \times 10^6$ (n=43)	$150-450 \times 10^6$ (n=69)
Median follow-up (min, max), months	20 (4, 35)	11 (3, 21)	4 (<1, 17)	6 (<1, 35)
Tumor response, n/N(%)				
ORR	10/12 (83)	6/14 (43)	24/33 (73)	40/59 (68)
sCR/CR	5 (42)	2 (14)	10 (30)	17 (29)
VGPR	5 (42)	3 (21)	7 (21)	15 (25)
PR	0	1 (7)	7 (21)	8 (14)
Median time to first response (min,max), months				
≥PR	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 2)
≥CR	6 (1, 24)	12 (6, 18)	1 (1, 13)	2 (1, 24)

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CAR-T cell persistence was observed in 27 of 30 patients with ongoing response and evaluable at three months, 20 of 23 patients with ongoing response and evaluable at six months, six of eleven patients with ongoing response and evaluable at twelve months, three of six patients with ongoing response and evaluable at 18 months, and two of two patients with ongoing response and evaluable at 24 months.

The adverse events observed with bb21217 were consistent with known toxicities of BCMA CAR T-cell therapies, with low rates of Grade  $\geq 3$  CRS and neurotoxicity. Of the 69 patients, 48 patients developed bb21217-related CRS: 45 with Grade 1/2, one with Grade 3, and two with Grade 5 (death). Eleven of 69 (16%) patients developed neurotoxicity; eight Grade 1/2, two Grade 3 (one with vertigo/dizziness and one with encephalopathy), and one Grade 4 (encephalopathy). One additional death occurred from infection within 6 months in the absence of MM progression. Cytopenias were common and not dose related. Grade  $\geq 3$  infections were reported in 26 % of patients (18 of 69).

#### ***Strategic collaborations in oncology***

We have formed and intend to seek other opportunities to form strategic collaborations with third parties who can augment our T cell immunotherapy, lentiviral vector and gene-editing expertise, and to access the substantial funding and other resources required to develop and commercialize T cell immunotherapy products. To date, we have focused on forging a limited number of significant strategic collaborations with leading pharmaceutical companies and academic research centers where both parties contribute expertise to enable the discovery and development of potential product candidates. Currently, our strategic collaborations in oncology include relationships with:

- BMS, in the development of ide-cel and bb21217 product candidates in multiple myeloma;
- Regeneron, in the discovery, development, and commercialization of novel cell therapies for cancer;
- Medigene AG, to discover TCR product candidates in the field of cancer; and
- Gritstone Oncology, Inc., to validate targets and discover TCR product candidates in the field of cancer.

We also have academic collaborations at various stages or research and preclinical development at the Seattle Children's Research Institute, University of North Carolina, and the Fred Hutchinson Cancer Research Center.

#### ***Our collaboration with BMS***

In March 2013, we began a strategic collaboration with Celgene, now BMS, to discover, develop and commercialize chimeric antigen receptor-modified T cells, or CAR T cells, as potentially disease-altering gene therapies in oncology, which was amended and restated in June 2015, and amended again in February 2016 and in September 2017. The multi-year research and development collaboration focused on applying our expertise in gene therapy technology to CAR T cell-based therapies, to target and destroy cancer cells. The research collaboration term ended in June 2018, with ide-cel and bb21217 product candidates arising from the collaboration.

In February 2016, BMS exercised its option with respect to the ide-cel product candidate, and we exclusively licensed to BMS the worldwide rights to develop and commercialize the ide-cel product candidate, while retaining an option to co-develop and co-promote the ide-cel product candidate in the United States. In connection with its exercise of its option to obtain an exclusive license, BMS paid to us an option fee in the amount of \$10.0 million. In March 2018, we exercised our option to co-develop and co-promote the ide-cel product candidate in the United States. Under the terms of the co-development and co-promotion agreement that we have with BMS for the development and commercialization of ide-cel, we share equally in all costs relating to developing, commercializing and manufacturing the product candidate within the United States and we would share equally in the United States profits. In 2019, BMS paid us a \$10.0 million clinical milestone payment.

In September 2017, BMS exercised its option with respect to the bb21217 product candidate, and we exclusively licensed to BMS the worldwide rights to develop and commercialize the bb21217 product candidate, while retaining an option to co-develop and co-promote the bb21217 product candidate in the United States on terms substantially similar to the co-development and co-promotion arrangement for the ide-cel product candidate. In connection with its exercise of its option to obtain an exclusive license, BMS paid to us an option fee in the amount of \$15.0 million. Under the terms of the license agreement with BMS for the exclusive rights to the development and commercialization of bb21217, we are and will be responsible for conducting and funding all research and development activities performed up through completion of the CRB-402 study. In 2019, the protocol was amended to enroll additional patients and BMS has agreed to reimburse us a specified amount for the additional patients.

In May 2020, we amended the co-development and co-promotion agreement with respect to ide-cel and the license agreement with respect to bb21217. Under these amended agreements, BMS was relieved of its obligations to pay us future ex-U.S. milestones and royalties on ex-U.S. sales for each of ide-cel and bb21217 in exchange for an up-front, non-refundable, non-creditable payment of \$200.0 million. In connection with these amendments, BMS assumed the contract manufacturing

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agreements relating to ide-cel adherent lentiviral vector. Over time, BMS is assuming responsibility for manufacturing ide-cel suspension lentiviral vector outside of the U.S., with bluebird responsible for manufacturing ide-cel suspension lentiviral vector in the United States. In addition, under these amended agreements, the parties are released from future exclusivity related to BCMA-directed T cell therapies. In addition, if we do not exercise our option to co-develop and co-promote the bb21217 product candidate in the United States, we are also eligible to receive up to \$10.0 million in clinical milestone payments, up to \$67.5 million in regulatory milestone payments and up to \$45.0 million in commercial milestone payments, as well as a percentage of net sales as a royalty in a range from the mid-single digits to low-teens. The royalties payable to us are subject to certain reductions, including for any royalty payments required to be made by BMS to acquire patent rights, with an aggregate minimum floor. BMS will assume certain development obligations and must report on their progress in achieving these milestones on a quarterly basis.

Our collaboration with BMS is governed by a joint governance committee, or JGC, formed by representatives from us and BMS. The JGC, among other activities, reviews and approves development and commercialization plans and budgets for activities in the United States. Either party may terminate the agreements upon written notice to the other party in the event of the other party's uncured material breach. BMS may terminate the agreement for any reason upon prior written notice to us. If the agreements are terminated, rights to product candidates in development at the time of such termination will be allocated to the parties through a mechanism included in the agreements. In addition, if BMS has the right to terminate any co-development and co-promotion agreement or license agreement for our breach, BMS may elect to continue such agreement however, any amounts payable by BMS to us under such agreement will be reduced.

#### ***Manufacturing in Oncology***

In November 2017, we purchased a partially completed manufacturing facility located in Durham, North Carolina for \$11.5 million. We acquired this 125,000 square foot facility to provide manufacturing capacity for our lentiviral vectors in support of our current and planned gene and cell therapy product candidates. In March of 2019, we announced the official opening of this facility, of which a portion has been placed into service and the remainder is in the process of construction. We currently expect that it will begin to produce lentiviral vector in 2021 in support of our oncology programs, including for ide-cel commercialization, if and when approval is obtained. In addition, we have entered into multi-year agreements with external manufacturing partners in the United States and Europe to support our various preclinical and clinical programs in oncology.

#### **Intellectual property**

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have developed or in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of gene therapy products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, certain genes, transgenes, methods of transferring genetic material into cells, genetically modified cells, processes to manufacture our lentivirus-based product candidates and other proprietary technologies and processes related to our lead product development candidates. As of January 31, 2021, our patent portfolio includes the following:

- approximately 182 patents or patent applications that we own or have exclusively in-licensed from third parties related to lentiviral vectors and vector systems;
- approximately 40 patents or patent applications that we have non-exclusively in-licensed from third parties related to lentiviral vectors and vector systems;

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- approximately 97 patents or patent applications that we own or have exclusively in-licensed from third parties, including 13 that are co-owned with MIT, related to vector manufacturing or production;
- approximately 194 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to therapeutic cellular product candidates;
- approximately 465 patents or patent applications that we own or have exclusively in-licensed or optioned from third parties related to oncology product candidates, including CAR T cell vector systems and manufacturing, T cell manufacturing, and therapeutic T cells;
- approximately 201 patents or patent applications that we own or have exclusively or co-exclusively in-licensed from third parties related to gene editing compositions and methods; and
- approximately 43 patent applications that we have non-exclusively in-licensed from third parties related to gene editing compositions and methods.

Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our gene therapy product candidates manufacturing processes. Examples of the products and technology areas covered by our intellectual property portfolio are described below. See also “License agreements.” From time to time, we also evaluate opportunities to sublicense our portfolio of patents and patent applications that we own or exclusively license, and we may enter into such licenses from time to time.

#### *Beti-cel and LentiGlobin for SCD*

The beti-cel and LentiGlobin for SCD programs include the following patent portfolios described below.

- Pasteur Institute.** The Pasteur patent portfolio contains patent applications directed to FLAP/cPPT elements and lentiviral vectors utilized to produce beti-cel and LentiGlobin for SCD. As of January 31, 2021, we had an exclusive license to two issued U.S. patents. We expect the issued composition of matter patents to expire in 2022 and 2023 in the United States (excluding possible patent term extensions).
- RDF.** The in-licensed patent portfolio from Research Development Foundation, or RDF, in part, contains patents and patent applications directed to aspects of our lentiviral vectors that may be utilized to produce beti-cel and LentiGlobin for SCD. As of January 31, 2021, we had an exclusive license (from RDF) to eight issued U.S. patents and two pending U.S. patent applications related to our lentiviral vector platform. Corresponding foreign patents and patent applications related to our lentiviral vector platform include pending applications or issued patents in Canada, Europe, and Israel. We expect the issued composition of matter patents to expire from 2021-2027 in the United States, and in 2022 in the rest of the world (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2021-2022 (worldwide, excluding possible patent term extensions).
- MIT/bluebird bio.** This co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral β-globin expression vectors. As of January 31, 2021, we co-owned four issued U.S. patents and one pending U.S. patent application, as well as corresponding foreign patents issued in Europe and Hong Kong. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2023 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2023 (worldwide, excluding possible patent term extensions). We note that we have an exclusive license to MIT’s interest in this co-owned intellectual property.
- Children’s Medical Center Corporation (CMCC)/bluebird bio.** This co-owned patent portfolio contains patent applications directed to certain specific compositions of matter for treating β-thalassemia and SCD. As of January 31, 2021, we co-owned one pending U.S. patent application, as well as nine corresponding foreign patent applications. We expect any composition of matter or methods patents, if issued from the pending patent applications, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We note that we have an option to exclusively license CMCC’s interest in this co-owned intellectual property.

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Our β-thalassemia and SCD research programs also include in-licensed patents and patent applications that are directed to certain specific compositions of matter and methods for treating β-thalassemia/SCD. As of January 31, 2021, we had an exclusive license to two issued U.S. patents and one pending U.S. patent application and as well as 25 corresponding foreign patents and 15 pending corresponding foreign applications. We expect the issued composition of matter patents to expire in 2035 in the United States and in the rest of the world (excluding possible patent term extensions). Further, we expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2021, we had a non-exclusive license to five issued U.S. patents, three pending corresponding foreign patent applications and 32 issued foreign patents. We expect the issued composition of matter and method patents to expire in 2029 in the United States and in the rest of the world (excluding possible patent term extensions). We expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2029 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2029 (worldwide, excluding possible patent term extensions).

***Eli-cel***

The eli-cel program includes the following patent portfolios described below.

- **Pasteur Institute.** The in-licensed Pasteur patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce eli-cel.
- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce eli-cel.

• **bluebird bio.** The bluebird bio patent portfolio contains patents and patent applications directed to compositions of matter for eli-cel vectors and compositions and methods of using the vectors and compositions in cell-based gene therapy of adrenoleukodystrophy or adrenomyeloneuropathy. As of January 31, 2021, we owned three U.S. patents and 26 issued foreign patents. We expect the issued composition of matter patents for eli-cel vectors to expire in 2032 (excluding possible patent term extensions). Further, we expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2032 (worldwide, excluding possible patent term extensions).

***Ide-cel, bb21217, and independent multiple myeloma program***

The multiple myeloma programs include the following patent portfolios described below.

- **Pasteur Institute.** The in-licensed Pasteur patent portfolio contains patents and patent applications described above that are directed towards aspects of our lentiviral vectors utilized to produce our product candidates for multiple myeloma.
- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of our lentiviral vectors utilized to produce our product candidates for multiple myeloma. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2021, we had an exclusive license (from RDF) to five issued patents related to our oncology platform. We expect the issued patents to expire from 2021-2022 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2021-2022 (worldwide, excluding possible patent term extensions).
- **Biogen.** The in-licensed patent portfolio from Biogen Inc., formerly Biogen Idec MA Inc. and referred to herein as Biogen, contains patents and patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2021, we had a co-exclusive license to five issued U.S. patents and one pending U.S. patent application and one pending corresponding foreign application and 49 issued corresponding foreign patents related to bb21217. We expect the issued patents to expire from 2024-2032 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2024-2030 (excluding

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possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2024-2030 (worldwide, excluding possible patent term extensions).

- NIH.** The in-licensed patent portfolio from NIH contains patents and patent applications directed towards aspects of T cell-based products that target BCMA. As of January 31, 2021, we had an exclusive license to 13 issued U.S. patents, 3 pending U.S. patent applications and 20 corresponding foreign patent applications and 19 issued corresponding foreign patents related to ide-cel. We expect the issued composition of matter patents to expire from 2033-2034 (excluding possible patent term extensions). We expect any other composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- bluebird bio.** The bluebird bio patent portfolio contains patents and patent applications directed to certain specific compositions of matter for generating CAR T cells. As of January 31, 2021, we owned seven issued U.S. patents, ten pending U.S. patent applications, 104 corresponding foreign patent applications, 181 foreign patents and one pending PCT application. We expect the issued composition of matter and methods patents to expire in 2035 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2035-2040 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035-2040 (worldwide, excluding possible patent term extensions).

**Lentiviral platform (e.g., vectors, manufacturing, and cell therapy products)**

The lentiviral platform, which is potentially applicable across our programs in severe genetic disease and oncology, includes the following patent portfolios described below.

- Pasteur Institute.** The Pasteur patent portfolio contains the patents and patent applications described above.

- RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above.

- SIRION.** The in-licensed patent portfolio from SIRION Biotech GmbH, or SIRION, contains patents and patent applications directed to methods of manufacturing ex vivo gene therapy products with a lentiviral vector. As of January 31, 2021, we had an exclusive license to two issued U.S. patents, one pending U.S. patent application and two corresponding foreign patent applications and issued corresponding foreign patents in Europe, Israel, and Japan. We expect the issued method patents to expire in 2033 (excluding possible patent term extensions). We expect any other composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- bluebird bio.** Another component of the bluebird bio patent portfolio includes the vector manufacturing platform and is potentially applicable across our severe genetic disease and oncology programs. This portion of the portfolio contains patents and patent applications directed to improved methods for transfection and transduction of therapeutic cells. As of January 31, 2021, we owned three issued U.S. patents, four pending U.S. patent applications and 40 corresponding foreign patent applications and 55 issued corresponding foreign patents. We expect the issued method patents to expire in 2032 (excluding possible patent term extensions). We expect composition of matter and method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2032-2038 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2032-2038 (worldwide, excluding possible patent term extensions).

**Oncology platform (e.g., vectors, manufacturing, and T cell-based products)**

Our T cell-based oncology platform and oncology research program, which is applicable to our multiple myeloma programs and other potential programs in cancer, includes the following patent portfolios described below.

- Pasteur Institute.** The Pasteur patent portfolio contains the patents and patent applications described above.

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**RDF.** The in-licensed RDF patent portfolio described above contains patents and patent applications that are also applicable to our oncology platform. In addition, the RDF portfolio contains additional patent applications directed to aspects of our oncology program. As of January 31, 2021, we had an exclusive license (from RDF) to five issued patents related to our oncology platform. We expect the issued patents to expire from 2021-2022 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2021-2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2021-2022 (worldwide, excluding possible patent term extensions).

**bluebird bio.** One aspect of the bluebird bio patent portfolio contains patent applications directed to certain specific compositions of matter for generating CAR T cells directed against various cancers and improved CAR T cell compositions. As of January 31, 2021, we owned three issued U.S. patents, 13 pending U.S. patent applications and 74 corresponding foreign patent applications and three foreign patents; six families of pending U.S. provisional applications; and nine pending PCT applications. We expect the issued composition of matter patent to expire in 2034 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2034-2041 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2034-2041 (worldwide, excluding possible patent term extensions).

**T Cell Manufacturing Methods License.** We have in-licensed patents and patent applications that are directed to certain specific methods for generating CAR T cells. As of January 31, 2021, we had a nonexclusive license to two issued U.S. patents, one pending U.S. patent application, and 30 corresponding issued foreign patents. We expect the issued method patents to expire in 2026 (excluding possible patent term extensions). Further, we expect methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2026 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2026 (worldwide, excluding possible patent term extensions).

**T Cell Immunotherapy Product Candidate Licenses.** We have in-licensed patents and patent applications that are directed to certain specific compositions of matter for generating CAR T cells directed against various cancers and related methods of treatment. As of January 31, 2021, we have an exclusive license to one issued U.S. patent and ten corresponding foreign patents and co-own a pending US application and seven corresponding foreign patent applications to a particular target antigen. We expect the issued composition of matter patent to expire in 2025 (excluding possible patent term extensions). We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2036 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2021, we have an exclusive license to three families of U.S. non-provisional applications and corresponding PCT applications directed to compositions and methods for treating cancers that express particular target antigens. We expect any composition of matter or method of use patents, if issued from a corresponding nonprovisional application or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2039 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2039 (worldwide, excluding possible patent term extensions). Also as of January 31, 2021, we co-own a PCT application directed to compositions and methods for treating cancers that express a particular antigen. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional applications or foreign applications, if applicable, and if the appropriate, renewal, annuity or other governmental fees are paid, to expire in 2040 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2040 (worldwide, excluding possible patent term extensions). Also as of January 31, 2021, we co-own three families of PCT applications directed to compositions and methods for treating cancers that express a particular antigen. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2040 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity,

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or other governmental fees are paid, to expire from 2040 (worldwide, excluding possible patent term extensions). Also as of January 31, 2021, we have an option to exclusively license two U.S. patent applications and 7 corresponding foreign patent applications that are directed to compositions and methods for treating cancers that express a particular antigen. We expect any composition of matter or methods patents, if issued from corresponding nonprovisional applications or foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2037-2039 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2037-2039 (worldwide, excluding possible patent term extensions).

***Gene editing platform (e.g., homing endonucleases, chimeric endonucleases, megaTALS, genetically modified cells)***

The gene editing platform includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.

- **RDF.** The in-licensed RDF patent portfolio described above may contain patents and patent applications that are potentially applicable to our gene editing platform.

- **Gene Editing License.** We in-licensed patent portfolios that contain patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our β-thalassemia, SCD, oncology and other programs. As of January 31, 2021, we had an exclusive/co-exclusive license to seven issued U.S. patents and one pending U.S. patent application and 27 corresponding foreign patents and three corresponding patent applications related to our gene editing platform. We expect the issued composition of matter patents to expire in 2030 (excluding possible patent term extensions). Further, we expect composition of matter or methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2030 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2030 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2021, we had an exclusive license to two issued U.S. patents and six corresponding foreign patents related to our gene editing platform. We expect the issued composition of matter patent to expire from 2027-2031 in the United States (excluding possible patent term extensions) and in 2027 in the rest of the world.

- **Academic Gene Editing Licenses.** We in-licensed patent portfolios from multiple academic medical centers, each portfolio containing patents and patent applications directed to aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our β-thalassemia, SCD, oncology and other programs. As of January 31, 2021, we had an exclusive license to four issued U.S. patents and three pending U.S. patent applications and 15 corresponding foreign patents and two corresponding patent applications related to our gene editing platform. We expect the issued patent to expire in 2027 (excluding possible patent term extensions) in the U.S. and from 2027-3032 in the rest of the world. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2027-2032 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2027-2032 (worldwide, excluding possible patent term extensions). As of January 31, 2021, we also had a non-exclusive license to one issued U.S. patent and one pending U.S. patent application related to our gene editing platform. We expect the issued composition of matter patent to expire in 2035 (excluding possible patent term extensions). We expect any other composition of matter or methods patents, if issued from corresponding nonprovisional applications or foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions). In addition, as of January 31, 2021, we had an exclusive license to one issued U.S. patent, and 20 corresponding issued foreign patents and 7 corresponding foreign patent applications related to our gene editing platform. We expect the issued composition of matter patents to expire in 2033 (excluding possible patent term extensions). We expect other composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions). As of January 31, 2021, we also had a non-exclusive license

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to two issued U.S. patents, one pending U.S. application, 25 corresponding foreign patent applications, and 13 corresponding foreign patents related to our gene editing platform. We expect the issued composition of matter patents to expire in 2033 (excluding possible patent term extensions). Further, we expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

**bluebird bio.** One aspect of the bluebird bio patent portfolio contains patent applications that are potentially applicable to certain aspects of our gene editing platform to produce genome modifying enzymes and genetically modified cells that are potentially applicable to our oncology and other programs. As of January 31, 2021, we owned 11 patent families that include one issued U.S. patent, 14 pending U.S. patent applications and 58 corresponding foreign patent applications related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2037-2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2037-2038 (worldwide, excluding possible patent term extensions). As of January 31, 2021, we owned three PCT applications related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2038-2039 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2038-2039 (worldwide, excluding possible patent term extensions). As of January 31, 2021, we also owned one provisional application related to our gene editing platform. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2041 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2041 (worldwide, excluding possible patent term extensions). As of January 31, 2021, we co-owned (with Cellectis SA) two issued U.S. patents, two corresponding foreign patent applications, and 17 corresponding foreign patents related to our gene editing platform. We expect composition of matter or method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2034 (excluding possible patent term extensions). We expect the other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2034 (worldwide, excluding possible patent term extensions).

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and third parties. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may

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otherwise become known or be independently discovered by competitors. To the extent that our consultants or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

#### **License agreements**

##### ***Inserm-Transfert***

In May 2009, we entered into an exclusive license with Inserm-Transfert, which is a wholly-owned subsidiary of Institut national de la santé et de la recherche médicale, for use of certain patents and know-how related to the ABCD1 gene and corresponding protein, for use in the field of human ALD therapy. Inserm-Transfert is referred to herein as Inserm. The last patent in the Inserm licensed patent portfolio expired in February of 2016. Inserm retains the right to practice the intellectual property licensed under the agreement for educational, clinical and preclinical studies purposes.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include eli-cel, we will be obligated to pay Inserm a percentage of net sales as a royalty for the longer of the life of any patents covering the product or 10 years from first commercial sale. This royalty is in the low single digits. The royalties payable to Inserm are subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

We are required to use all commercially reasonable efforts to develop licensed products and introduce them into the commercial market as soon as practical, consistent with our reasonable business practices and judgment in compliance with an agreed upon development plan. We have assumed certain development, regulatory and commercial milestone obligations and must report on our progress in achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement at any time. Either party may terminate the agreement in the event of the other party's material breach which remains uncured after 60 days of receiving written notice of such breach or in the event the other party becomes the subject of a voluntary or involuntary petition in bankruptcy and such petition is not dismissed with prejudice within 120 days after filing. In addition, Inserm may terminate the license agreement in the event that we cannot prove within 60 days of written notice from Inserm that we have been diligent in developing the licensed products and introducing them into the commercial market.

Absent early termination, the agreement will automatically terminate upon the expiration of all issued patents and filed patent applications within the patent rights covered by the agreement or 10 years from the date of first commercial sale of a licensed product, whichever is later. The license grant ceases in connection with any such termination. The longest lived patent rights licensed to us under the agreement expired in 2016.

##### ***Institut Pasteur***

We have entered into a license with Institut Pasteur for certain patents relating to the use of DNA sequences, lentiviral vectors and recombinant cells in the field of *ex vivo* gene therapy and CAR T cell-based therapy in a range of indications, excluding vaccinations. This agreement was amended twice in 2012, again in 2013 and most recently in 2015. The Institut Pasteur licensed patent portfolio includes two U.S. patents. The issued patents have statutory expiration dates in 2022 and 2023. The license is exclusive for products containing human and non-human lentiviral vectors. Institut Pasteur retains the right, on behalf of itself, its licensees and research partners, to conduct research using the licensed intellectual property.

We have the right to grant sublicenses outright to third parties under the agreement. For the first sublicense including a product targeting β-hemoglobinopathies (including β-thalassemia and SCD) or ALD (including CALD and adrenomyeloneuropathy), we must pay Institut Pasteur an additional payment of €3.0 million. If we receive any income (cash or non-cash) in connection with sublicenses for products targeting indications other than β-hemoglobinopathies (including β-thalassemia and SCD) or ALD (including CALD and adrenomyeloneuropathy ), we must pay Institut Pasteur a percentage of such income varying from low single digits if the sublicense also includes licenses to intellectual property controlled by us, and a percentage of sublicense income in the mid-range double digits if the sublicense does not include licenses to intellectual property controlled by us.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, LentiGlobin for SCD, eli-cel, ide-cel and bb21217, we will be obligated to pay Institut Pasteur a percentage of net sales as a royalty. This royalty varies depending on the indication of the product but in any event is in the low single digits. In addition, starting in 2016 we must make under this agreement an annual maintenance payment which is creditable against royalty payments on a year-by-year basis. If the combined royalties we would be required to pay to Institut Pasteur and third parties is higher than a pre-specified percentage, we may ask Institut Pasteur to re-negotiate our royalty rates under this relationship.

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We are required to use all reasonable commercial efforts (as compared to a company of similar size and scope) to develop and commercialize one or more products in the license field and to obtain any necessary governmental approvals in respect of, and market the products in license field, if any. Additionally, we have assumed certain development and regulatory milestone obligations. We must report on our progress towards achieving these milestones on an annual basis. We may unilaterally terminate the license agreement at any time by sending Institut Pasteur 90 days prior written notice. Either party may terminate the license in the event of the other party's substantial breach which remains uncured after 60 days of receiving written notice of such breach. Institut Pasteur may also terminate the agreement in the event bankruptcy proceedings are opened against us and not dismissed within 60 days.

Absent early termination, the agreement will automatically terminate upon the expiration of the last licensed patents or five years after first market authorization of the first product, whichever occurs later. In the event the agreement is terminated, while the license grant would cease, we would retain the right to manufacture, import, use and sell licensed products for a certain period of time post-termination. In addition, our ownership stake in certain jointly made improvements covered by the licensed patents would survive termination of the agreement. The longest lived patent rights licensed to us under the agreement are currently expected to expire in 2023.

#### ***Stanford University***

In July 2002, we entered into a non-exclusive license agreement with the Board of Trustees of the Leland Stanford Junior University, referred to herein as Stanford, which we amended and restated in April 2012. Under this agreement, we are granted a license to use the HEK293T cell line for any commercial or non-commercial use for research, nonclinical and clinical development purpose and human and animal gene therapy products.

We have the right to grant sublicenses outright to third parties under the agreement. For each such sublicense we grant, we must pay Stanford a fee (unless the sublicense is to a collaborating partner, contract manufacturer or contract research organization).

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, LentiGlobin for SCD, eli-cel, ide-cel and bb21217, we will be obligated to pay Stanford a percentage of net sales as a royalty. This royalty varies with net sales but in any event is in the low single digits and is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage which is less than one percent. Since April 2013, we have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.

We may unilaterally terminate the agreement by giving Stanford 30 days' written notice. Stanford may also terminate the license agreement if after 30 days of providing notice we are delinquent on any report or payment, are not using commercially reasonable efforts to develop, manufacture and/or commercialize one or more licensed products, are in material breach of any provision or provide any false report. Termination of this agreement may require us to utilize different cell types for vector manufacturing, which could lead to delays.

Absent early termination, the license will expire in April 2037. We may elect to extend the term for an additional 25 years so long as we have a commercial product on the market at that time and we are in material compliance with the license agreement.

#### ***Massachusetts Institute of Technology***

In December 1996, we entered into an exclusive license with the Massachusetts Institute of Technology, referred to herein as MIT, for use of certain patents in any field. This license agreement was amended in December 2003, May 2004 and June 2011. The licensed patent portfolio includes at least 13 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date from in 2023. This license also has been amended to include a case jointly owned by MIT and us wherein we received the exclusive license to MIT's rights in this case. MIT retains the right to practice the intellectual property licensed under the agreement for noncommercial research purposes.

We have the right to grant sublicenses outright to third parties under the agreement. In the event we sublicense the patent rights, we must pay MIT a percentage of all payments we receive from by the sublicensee. This percentage varies from mid-single digits to low double digits.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel and LentiGlobin for SCD, we will be obligated to pay MIT a percentage of net sales by us or our sublicensees as a royalty. This royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one-percent. In addition, we make under this agreement an annual maintenance payment which may be credited against the royalty payments.

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We are required to use diligent efforts to market licensed products and to continue active, diligent development and marketing efforts for licensed products during the term of the agreement. We have assumed certain milestones with respect to raising capital investment and regulatory progress. We must report on our progress on achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement upon six months' notice to MIT. MIT may terminate the agreement if we cease to carry on our business, or in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment). In the event the agreement is terminated, while the license grant would cease, we would retain a right to complete manufacture of any licensed products in process and sell then-existing inventory. In addition, MIT would grant our sublicensees a direct license following such termination. With respect to jointly owned intellectual property, any termination would allow MIT to grant licenses to any third-party to such intellectual property, without our approval, unless a sublicensee was already in place, in which case, MIT would grant our sublicensees a direct license.

#### ***Research Development Foundation***

In December 2011, we entered into an exclusive license with RDF to use certain patents that involve lentiviral vectors. The RDF licensed patent portfolio includes at least 31 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2021 and 2027. RDF retains the right, on behalf of itself and other nonprofit academic research institutions, to practice and use the licensed patents for any academic, non-clinical research and educational purposes. We have the right to grant sublicenses outright to third parties under the agreement.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, LentiGlobin for SCD, eli-cel, ide-cel and bb21217, we are obligated to pay RDF a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced by half if during the following ten years from the first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

We are required to use commercially reasonable and diligent efforts for a company of our size and resources to develop or commercialize one or more licensed products, including our first licensed product by 2016 and a second licensed product by 2018. These diligence efforts include minimum annual royalty payments to RDF, which are creditable against earned royalties otherwise due to RDF, and payments upon regulatory milestones.

RDF may terminate the agreement in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment) or in the event we become bankrupt, our business or assets or property are placed in the hands of a receiver, assignee or trustee, we institute or suffer to be instituted any procedure in bankruptcy court for reorganization or rearrangement of our financial affairs, make a general assignment for the benefit of creditors, or if we or an affiliate or a sublicensee institutes any procedure challenging the validity or patentability of any patent or patent application within the licensed patents, the agreement will immediately terminate.

Absent early termination, the agreement will continue until its expiration upon the later of there being no more valid claims within the licensed patents or the expiration of our royalty obligations on licensed products that are subject to an earned royalty, if such earned royalty is based on the minimum 10-year royalty period described above. In the event the agreement is terminated, while the license grant would cease, RDF will grant our sublicensees a direct license. The longest lived patent rights licensed to us under the agreement are in one U.S. patent currently expected to expire in 2027.

#### ***Biogen***

In August 2014, we entered into a license agreement with Biogen, pursuant to which we co-exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2024 and 2032. Biogen retains the right to practice and use the licensed patents in the licensed field and territory. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include ide-cel and bb21217, we will be obligated to pay Biogen a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$24.0 million in the aggregate for each licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to Biogen. Either party may terminate the license in the event of the other party's material breach upon notice and an opportunity for the breaching party to cure. Either party may also terminate the agreement in the event bankruptcy proceedings are opened against the other party and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically

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terminate upon the expiration of all patent rights covered by the agreement or ten years from the date of first commercial sale of a licensed product, whichever is later. The longest lived patent rights licensed to us under the Agreement are in a U.S. patent, currently expected to expire in 2032.

***NIH***

In August 2015, we entered into a license agreement with the NIH, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of T cell-based products that target BCMA. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033-2034. NIH retains the right to practice the intellectual property licensed under the agreement on behalf of the government of the United States. We have the right to grant sublicenses to third parties, subject to certain conditions. For each such sublicense we grant we must pay the NIH a fee. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include ide-cel and bb21217, we will be obligated to pay the NIH a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement. Additionally, we have assumed certain development and regulatory milestone obligations and must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$9.7 million in the aggregate for a licensed product upon the achievement of these milestones. We may unilaterally terminate the license agreement at any time with prior written notice to the NIH. The NIH may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. The NIH may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of the patent rights covered by the agreement. The longest lived patent rights licensed to us under the Agreement are currently expected to expire in 2034.

***SIRION***

In December 2015, we entered into a license agreement with SIRION, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of manufacturing gene therapy products. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel and LentiGlobin for SCD, we will be obligated to pay SIRION a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement, and we must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to \$13.4 million in the aggregate upon the achievement of certain development and regulatory milestones. We may unilaterally terminate the license agreement at any time with prior written notice to SIRION. SIRION may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. SIRION may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of the patent rights covered by the agreement. The longest lived patent rights licensed to us under the Agreement are currently expected to expire in 2033.

***Orchard Therapeutics Limited***

In April 2017, we entered into a license agreement with GlaxoSmithKline Intellectual Property Development Limited, or GSK, pursuant to which GSK non-exclusively licensed certain of our patent rights related to lentiviral vector technology to develop and commercialize gene therapies for Wiscott-Aldrich syndrome and metachromatic leukodystrophy, two rare genetic diseases. Effective April 2018, this license agreement was assigned by GSK to Orchard Therapeutics Limited, or Orchard. Financial terms of the agreement included an upfront payment to us as well as potential development and regulatory milestone payments and low single digit royalties on net sales of covered products.

***Competition***

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. Not only must we compete with other companies that are focused on gene therapy products but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future. Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any

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treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payers.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products. Depending on how successful these competitive efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, and our preclinical T cell-based cancer immunotherapy product candidates. These efforts include the following:

**$\beta$ -thalassemia** - The current standard of care for the treatment of  $\beta$ -thalassemia in the developed world is chronic blood transfusions to address the patient's anemia. In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with their chronic blood transfusions. Novartis and Chiesi, who provide the leading iron chelation therapies, are seeking to develop improvements to their product profile and accessibility. A number of different approaches are under investigation that seek to improve the current standard of care treatment options, including a protein that aims to improve red blood cell production and small molecule that aims to improve red blood cell metabolism. Reblozyl (luspatercept), a subcutaneously-delivered protein therapeutic marketed by Acceleron Pharma, Inc. and BMS that targets molecules in the TGF- $\beta$  superfamily, has been approved in the United States for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions, and was recently approved in the EU for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassemia. Additionally, Agios has announced that mitapivat, an oral pyruvate kinase receptor activator, will be entering phase 3 evaluations in 2H 2021. Some patients with  $\beta$ -thalassemia receive HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. In addition, there are a number of academic and industry-sponsored research and development programs to improve the outcomes of allogeneic HSCT, or the tolerability and safety of haploidentical HSCT, while increasing the availability of suitable donors. There are also several different groups developing gene therapy options for  $\beta$ -thalassemia. These include: CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated) is conducting an ongoing phase 1/2 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer; Sangamo BioSciences Inc. (in collaboration with Bioverativ Inc., a Sanofi company) is investigating ST-400, using a zinc finger nuclease-mediated gene-editing approach currently in an ongoing phase 1/2 study; and the San Raffaele Telethon Institute for Gene Therapy (in collaboration with Orchard Therapeutics) is currently investigating its gene therapy in a phase 2 study of adults and pediatric patients with transfusion dependent  $\beta$ -thalassemia (TDT), though Orchard Therapeutics has announced that this program has been deprioritized as of May 2020.

**Sickle cell disease** - The current standard of care for the treatment of SCD in the developed world is chronic blood transfusions or hydroxyurea (a generic drug). In addition, patients treated with chronic blood transfusions often receive iron chelation therapy to help manage the iron overload. We are aware of ongoing studies that continue to evaluate the efficacy and safety of hydroxyurea in various populations. In addition, a limited number of patients with SCD receive allogeneic HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. There are a number of academic and industry-sponsored research and development programs to improve the tolerability and safety of allogeneic HSCT with less well-matched sources of donor cells, while increasing the availability of suitable donors. Emmaus Life Sciences, Inc. received FDA approval for and have launched Endari (L-glutamine) for the treatment of SCD. In addition to the FDA approved hemoglobin S (HbS) polymerization inhibitor (voxelotor, Global Blood Therapeutics, Inc.) and the FDA / EMA approved antibody to p-selectin (crizanlizumab, Novartis), a number of different therapeutic approaches for the chronic treatment of SCD are under investigation targeting the various aspects of SCD pathophysiology, including: Pyruvate Kinase-R (PKR) activator, FT-4202, in a phase 1 study supported by Forma Therapeutics, a PDE9 inhibitor, IMR-687, in a phase 2 study supported by IMARA Inc., a pyruvate kinase receptor activator, mitapivat, in a phase 1 study supported by Agios Pharmaceuticals, Inc.. There are also several different groups developing gene therapy options for Sickle Cell Disease. These include: CRISPR Therapeutics AG's (in collaboration with Vertex Pharmaceuticals Incorporated) ongoing phase 1/2 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer, Aruvant Sciences, Inc.'s

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ongoing phase 1/2 study for its ARU-1801, which leverages a lentiviral vector encoding  $\gamma$ -globin., Editas Medicine, Inc.'s ongoing phase 1/2 study for its EDIT-301, which leverages the CRISPR/Cas12a gene editing platform to target the HBG1/2 promoter to upregulate HbF, and Graphite Bio's ongoing phase 1/2 study for its GPH101, which leverages a gene correction platform (CRISPR / homology directed repair (HDR)) to restore normal hemoglobin production . There are several other groups developing gene therapy approaches for SCD in early phases of development, including Beam Therapeutics, CSL Behring, Intellia Therapeutics, Inc. (in collaboration with Novartis), and Children's Hospital of Philadelphia (CHOP).

**CALD** - The current standard of care for the treatment of CALD is allogeneic HSCT. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT, such as Magenta Therapeutic, Inc.'s cord blood expansion technology which is currently being investigated in a phase 2 clinical trial for the treatment of inherited metabolic disorders, including adrenoleukodystrophy. Other possible treatments being investigated include Orpheris, Inc.'s OP-101, Minoryx Therapeutics' MIN-102 (leriglitazone), and Viking Therapeutics' VK0214.

**Multiple Myeloma** - The current standard of care for relapsed and refractory multiple myeloma includes IMIDs (e.g., thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), monoclonal antibodies (e.g., daratumamab, elotuzumab), cytotoxic agents, and HSCT. There are several groups developing autologous T cell therapies for relapsed and refractory multiple myeloma that use a similar autologous *ex vivo* approach, but a different target antigen, BCMA single-chain variable fragment or, we believe, cell processing techniques. These programs include: an anti-BCMA CAR T cell therapy that is in a phase 1b/2 study in the United States (Nanjing Legend in collaboration with Janssen Biotech); an anti-BCMA CAR T cell therapy that is in phase 1 study (Poseida Therapeutics, Inc.); an anti-BCMA CAR T cell therapy in clinical development (phase 1/2) sponsored by BMS following the completion of its acquisition of Juno Therapeutics, Inc and an anti-BCMA CAR T cell therapy that is in phase I study (Innovent Biologics Inc). In addition to these autologous T cell-based approaches, Allogene Therapeutics, Inc., Poseida, and CRISPR Therapeutics have disclosed preclinical programs for allogeneic BCMA CAR T cell therapies. There are also therapies using other modalities being developed by several groups, including multiple bispecific T cell engagers, including programs currently in clinical studies supported by Amgen Inc., Regeneron, Janssen Research and Development, LLC, BMS, as well as a specific antibody therapy currently in a phase 1 study supported by Pfizer, Inc., and an antibody drug conjugate therapy supported by GSK that underwent a BLA submission, and those being developed in preclinical programs.

**T cell-based immunotherapies in oncology** - Hundreds of academic laboratories, biotechnology and pharmaceutical companies are researching and developing T cell-based immunotherapies in oncology, in addition to the multiple myeloma programs described above. These include and are not limited to Novartis AG, Adaptimmune Inc., Bristol-Myers Squibb Inc., Gilead Sciences, Inc., Pfizer Inc., Amgen, Inc., Sanofi and Takeda among others. Many of the T cell-based immunotherapy programs being developed by these companies are in phase 1/2 clinical trials for multiple indications. Cancer therapies in other modalities, such as bispecific antibodies, antibody-drug conjugates, and dendritic cell vaccines, as well as combinatorial approaches are also in development across a wide range of targets.

### **Government regulation**

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. FDA approval must be obtained before clinical testing of biological products, and each clinical study protocol for a gene therapy product is reviewed by the FDA. FDA approval also must be obtained before marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research, or the CBER, regulates gene therapy products. The CBER works closely with the NIH. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from successfully commercializing our product or any future products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

[Table of Contents](#)***U.S. biological products development process***

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, in the past, a protocol and related documentation was submitted to and the study was registered with the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Pursuant to the current NIH Guidelines, research involving recombinant or synthetic nucleic acid molecules must be approved by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. Such trials remain subject to FDA and other clinical trial regulations, and only after FDA, IBC, and other relevant approvals are in place can these protocols proceed.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an IRB at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in

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relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed.

Human clinical studies are typically conducted in three sequential phases that may overlap or be combined:

- phase 1.* The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

- phase 2.* The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

- phase 3.* Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Post-approval clinical studies, sometimes referred to as phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, phase 2 and phase 3 clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical studies, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

#### ***U.S. review and approval processes***

After the completion of clinical studies of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, as amended, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and

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effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, withdraw the application, or request a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as phase 4 clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of standard BLAs in 10 months and 90% of priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

#### ***Orphan drug designation***

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Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

#### ***Expedited development and review programs***

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

#### ***Regenerative medicine advanced therapies designation***

As part of the 21st Century Cures Act, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine advanced therapies do not include those human cells, tissues, and cellular and tissue based

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products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval.

#### ***Post-approval requirements***

Maintaining compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to GMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of ZYNTEGLO and any future products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the GMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of GMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval. In addition, companies that manufacture or distribute drug or biological products or that hold approved BLAs must comply with other regulatory requirements, including submitting annual reports, reporting information about adverse drug experiences, and maintaining certain records. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, including a REMS or the conduct of post-marketing studies to assess a newly-discovered safety issue.

We also must comply with the FDA's and other jurisdictions' advertising and promotion requirements, such as those related to direct-to-consumer advertising and advertising to healthcare professionals, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. Consequences could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with healthcare

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professionals, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

***U.S. patent term restoration and marketing exclusivity***

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

***Healthcare and Privacy Laws***

In addition to restrictions on marketing of pharmaceutical products, several other types of state/ federal laws and trade association membership codes of conduct have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include Anti-Kickback and false claims statutes. The U.S. federal healthcare program Anti-Kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any healthcare item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. A person or entity need not have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging healthcare professionals or patients as speakers or consultants, may be subject to scrutiny if they do not fit squarely within the exemption or safe harbor.

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Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient assistance programs.

The U.S. federal civil False Claims Act prohibits, among other things, any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using, or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to “cause” the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery. In recent years, several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for, among other things, allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have faced enforcement actions for causing false claims to be submitted because of the company’s marketing the product for unapproved, and thus non-reimbursable, uses. Federal enforcement agencies also have showed increased interest in pharmaceutical companies’ product and patient assistance programs, including reimbursement and co-pay support services, and a number of investigations into these programs have resulted in significant civil and criminal settlements. In addition, the Affordable Care Act amended federal law to provide that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Criminal prosecution is possible for making or presenting a false or fictitious or fraudulent claim to the federal government.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created several new federal crimes, including healthcare fraud and false statements relating to healthcare matters. The healthcare fraud statute prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The U.S. federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to engage in extensive tracking of payments and other transfers of value to prescribers and teaching hospitals, including physician ownership and investment interests, and public reporting of such data. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children’s Health Insurance Program are required to track such payments, and must submit a report on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year. A number of other countries, states and municipalities have also implemented additional payment tracking and reporting requirements, which if not done correctly may result in additional penalties.

In addition, the U.S. Foreign Corrupt Practices Act, or the FCPA, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any official of another country, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in that capacity. In many other countries, healthcare professionals who prescribe pharmaceuticals are employed by government entities, and the purchasers of pharmaceuticals are government entities. Our dealings with these prescribers and purchasers may be subject to the FCPA.

Other countries, including a number of EU member states, have laws of similar application, including anti-bribery or anti-corruption laws such as the UK Bribery Act. The UK Bribery Act prohibits giving, offering, or promising bribes to any person, as well as requesting, agreeing to receive, or accepting bribes from any person. Under the UK Bribery Act, a company that carries on a business or part of a business in the United Kingdom may be held liable for bribes given, offered or promised to any person in any country by employees or other persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability under the UK Bribery Act is strict, but a defense of having in place adequate procedures designed to prevent bribery is available.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to

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business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In California the California Consumer Protection Act ("CCPA"), which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. While clinical trial data and information governed by HIPAA are currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope.

The majority of states also have statutes or regulations similar to the federal anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Several states now require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. In addition, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers, marketing expenditures, and drug pricing information. Certain state and local laws require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the European Union General Data Protection Regulation, also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these various healthcare and privacy laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have material adverse effects on our business, financial condition and results of operations. In the event governmental authorities conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare and privacy laws and regulations, they may impose sanctions under these laws, which are potentially significant and may include civil monetary penalties, damages, exclusion of an entity or individual from participation in government health care programs, criminal fines and imprisonment, as well as the potential curtailment or restructuring of our operations. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

#### ***Government regulation outside of the United States***

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical study may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The EMA has established the Adaptive Pathways pilot program intended to expedite or facilitate either an initial approval of a medicinal product in a well-defined patient subgroup with a high medical need and subsequent iterative expansion of the indication to a larger patient population, or an early regulatory approval (e.g., conditional approval), which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on a medicinal product's use in patients. The approach builds in regulatory processes already in place within the existing EU legal framework.

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The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application during such eight-year period starting from the date of grant of the innovative medicinal product's marketing authorization. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity (and the grant of the relevant generic or biosimilar marketing authorization). However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union and being granted a marketing authorization for an orphan medicinal product can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union where the application for a marketing authorization includes the results of all studies conducted in accordance with an agreed pediatric investigation plan for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation itself does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

In the EU, the advertising and promotion of our products will also be subject to EU member states' laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, as well as other EU member state legislation that may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's approved labeling. The off-label promotion of medicinal products is prohibited in the EU. The applicable laws at the EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict communications concerning the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with healthcare professionals.

Failure to comply with the EU member state laws implementing the Community Code on medicinal products, and EU rules governing the promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices, with the EU member state laws that apply to the promotion of medicinal products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements can result in enforcement action by the EU member state authorities (or in addition, in some member states, enforcement action from industry bodies or legal action from competitors), which may include any of the following: fines, imprisonment, orders forfeiting products or prohibiting or suspending their supply to the market, or requiring the manufacturer to issue public warnings, or to conduct a product recall.

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The national laws of certain EU member states require payments made to physicians to be publicly disclosed. Moreover, the European Federation of Pharmaceutical Industries and Associations, or EFPIA, Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organizations imposes a general obligation on members of the EFPIA or related national industry bodies to disclose transfers of value to healthcare professionals. In addition, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her competent professional organization, and/or the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU member states.

For other countries outside of the EU, such as countries in Eastern Europe, Central and South America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. This act could have implications for our interactions with physicians in and outside the UK. In all cases, again, the clinical trials are conducted in accordance with GCP, applicable regulatory requirements, and ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, warning letters or untitled letters, injunctions, civil, administrative, or criminal penalties, monetary fines or imprisonment, suspension or withdrawal of regulatory approvals, suspension of ongoing clinical studies, refusal to approve pending applications or supplements to applications filed by us, suspension or the imposition of restrictions on operations, product recalls, the refusal to permit the import or export of our products or the seizure or detention of products.

**Pricing, Coverage and Reimbursement**

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payers, including governments. In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payers. Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer. Third-party payers can include government healthcare systems, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payers may provide coverage, but place stringent limitations on such coverage, such as requiring alternative treatments to be tried first. These third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety, efficacy, and overall value. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. Our product candidates may not be considered medically reasonable or necessary or cost-effective. Even if a drug product is covered, a payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the United States and foreign governments continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of drug products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate systems under which products may be marketed only after a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of studies or analyses of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to set their own prices for medicines, but exert cost controls in other ways, including but not limited to, placing revenue caps on product sales, providing reimbursement for only a subset of eligible patients, mandating price negotiations after a set period of time, or mandating that prices not exceed an average basket of prices in other countries. The downward pressure on health care costs in general, particularly treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, European

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governments may periodically review and decrease prices based on factors, including but not limited to, years-on-market, price in other countries, competitive entry, new clinical data, lack of supporting clinical data, or other factors.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payers fail to provide adequate coverage and reimbursement. In addition, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

We have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as for ZYNTEGLO. While we are engaged in discussions with potential payers, there is no assurance that these payment models will be widely adopted by payers. Even with these payment models, there may be substantial resistance to the cost of our products by payers and the public generally. These payment models may not be sufficient for payers to grant coverage, and if we are unable to obtain adequate coverage for our products, the adoption of our products and access for patients may be limited. In addition, to the extent reimbursement for our products is subject to outcomes-based arrangements, our future revenues from product sales will be more at risk. These factors could affect our ability to successfully commercialize our products and adversely impact our business, financial condition, results of operations and prospects.

### **COVID-19**

Beginning in late 2019, the outbreak of a novel strain of coronavirus (COVID-19) has evolved into a global pandemic. As a result, we continue to experience disruptions and increased risk in our operations and those of third parties upon whom we rely, which may materially and adversely affect our business. These include disruptions and risks related to the conduct of our clinical trials, manufacturing, and commercialization efforts, as policies at various clinical sites and federal, state, local and foreign laws, rules and regulations continue to evolve, including quarantines, travel restrictions, and direction of healthcare resources toward pandemic response efforts. We continue to evaluate the impact of the COVID-19 global pandemic on patients, healthcare providers and our employees, as well as our operations and the operations of our business partners and healthcare communities. In response to the COVID-19 pandemic, we have implemented policies at our locations to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory or manufacturing facility, a work-from-home policy applicable to the majority of our personnel, and a phased approach to bringing personnel back to our locations over time. Given the importance of supporting our patients, we are diligently working with our suppliers, healthcare providers and partners to provide patients with access to ZYNTEGLO, while taking into account regulatory, institutional, and government guidance, policies and protocols. Further, we are working with our clinical study sites to understand the duration and scope of the impact on enrollment, develop protocols to help mitigate the impact of the COVID-19 pandemic, and other activities for our ongoing clinical studies. Refer to Management's Discussion and Analysis of Financial Condition and Results of Operations (Part II, Item 7 of this Form 10-K) for further discussion regarding the impact of COVID-19 on our fiscal year 2020 financial results.

The extent to which the COVID-19 pandemic impacts our business going forward will depend on numerous evolving factors we cannot reliably predict, including the duration and scope of the pandemic; governmental, business, and individuals' actions in response to the pandemic; and the impact on economic activity including the possibility of recession or financial market instability. Refer to Risk Factors (Part I, Item 1A of this Form 10-K) for a discussion of these factors and other risks.

### **Human capital**

As of January 31, 2021, we had 1,213 full-time employees, 223 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 750 employees are engaged in research and development activities and 463 employees are engaged in commercial, finance, legal, business development, human resources, information technology, facilities and other general administrative functions. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

### **Compensation and benefits programs**

Our compensation programs are designed to align our employees' interests with the drivers of growth and stockholder returns by supporting the Company's achievement of its primary business goals. The Company's goal is to attract and retain employees whose talents, expertise, leadership, and contributions are expected to sustain growth and drive long-term stockholder value. Consequently, we provide employee wages that are competitive within our industry, and we engage a nationally-recognized outside compensation and benefits consulting firm to independently evaluate the effectiveness of our compensation and benefit programs and to provide benchmarking against our peers within the industry. We seek to align our

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employees' interests with those of stockholders by linking annual changes in compensation to overall Company performance, as well as each individual's contribution to the results achieved. The emphasis on overall Company performance is intended to align the employee's financial interests with the interests of shareholders. We are also committed to providing comprehensive benefit options and it is our intention to offer benefits that will allow our employees and their families to live healthier and more secure lives. All employees are eligible for medical, dental, and vision insurance, paid and unpaid leaves, employee stock purchase plan, 401(k) plan, and group life and disability coverage.

#### ***Employee development and training***

The development, recruitment and retention of our employees is a critical success factor for our company. To ensure we provide a meaningful experience for our employees, we regularly measure organizational culture and engagement to build on the competencies that are important for our future success. We have a robust talent and succession planning process and have established programs to support the talent pipeline for critical roles throughout our organization, to help us identify, foster, and retain high performing employees. To empower our employees to realize their potential at bluebird, we provide a range of development programs, opportunities and resources they need to be successful, including leveraging formal leadership training and coaching to improve performance and retention, increase our organizational learning and support the promotion of our current employees.

#### ***Diversity***

We are committed to taking action to help address racial injustice and inequality. With significant input from employees and leaders at bluebird, our senior leadership team and board of directors has developed a set of commitments to help improve representation and culture of inclusion by pledging to accomplish the following by 2025:

- Double our Black, Indigenous, and Latino employee population;
- Balance our executive leadership and board of directors to ensure 50% representation of women and people of color; and
- Sustain 100% pay equity and increase representation of women and people of color across all levels.

#### ***Corporate Information***

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. Our mailing address and executive offices are located at 60 Binney Street, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. We maintain an Internet website at the following address: [www.bluebirdbio.com](http://www.bluebirdbio.com). The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

#### ***Item 1A. Risk Factors***

*An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.*

*Our business may be materially and adversely affected by the ongoing COVID-19 pandemic. The COVID-19 pandemic has had, and will likely continue to have, an impact on various aspects of our business and that of third parties on which we rely. The extent to which the COVID-19 pandemic impacts our business will depend in part on future developments, which are uncertain and unpredictable in nature.*

In December 2019, a novel strain of coronavirus (COVID-19) was reported and in March 2020, the World Health Organization characterized COVID-19 as a pandemic. The COVID-19 pandemic, which has continued to spread, and the related adverse public health developments, including orders to shelter-in-place, travel restrictions, and the imposition of additional requirements on businesses, have adversely affected workforces, organizations, healthcare communities, economies,

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and financial markets globally, leading to an economic downturn and increased market volatility. It has also disrupted the normal operations of businesses across industries, including ours. As a result of the COVID-19 pandemic, we are experiencing disruptions in our operations and business, and those of third parties upon whom we rely. For instance, we are experiencing disruptions in the conduct of our clinical trials, manufacturing and commercialization efforts, including the treatment of patients in the commercial context. We cannot reasonably assess or predict at this time the full extent of the negative impact that the COVID-19 pandemic and related effects may have on our business, financial condition, results of operations and cash flows. We expect to continue experiencing these disruptions in our operations and those of our third parties for an unknown period of time, as the trajectory of the COVID-19 pandemic remains uncertain and continues to evolve in the United States and globally. These impacts, which may materially and adversely affect our business, include the following:

- We are conducting a number of clinical studies across our programs in geographies which are affected by the COVID-19 pandemic. The COVID-19 pandemic has had, and will likely continue to have, an impact on various aspects of our clinical studies. Policies at various clinical sites and federal, state, local and foreign laws, rules and regulations are continuing to evolve, including through the implementation of quarantines and travel restrictions, and direction of healthcare resources toward pandemic response efforts. For instance, the availability of intensive care unit beds and related healthcare resources available to support activities unrelated to COVID-19 response have fluctuated with the incidence of severe cases of COVID-19 in the surrounding communities, and we anticipate that the availability of healthcare resources will continue to fluctuate and may become significantly constrained, with variability across geographies. The COVID-19 pandemic has disrupted the conduct of our ongoing clinical studies, with the result of slower patient enrollment and treatment as well as delays in post-treatment patient follow-up visits, the impact of which has varied by clinical study, with the most significant impacts being on our ongoing HGB-210 study for LentiGlobin for SCD. It is possible that these delays may impact the timing of our regulatory submissions. It is unknown how long these disruptions could continue. Moreover, we are commercializing ZYNTEGLO in Europe, and our ability to generate meaningful product revenue may be delayed. In addition to the constraints on healthcare systems and resources described above, which are also applicable in the commercial treatment context, we may experience decreased patient demand for our approved product during this period of disruption and increased uncertainty because potential patients may choose not to undergo treatment, or to delay treatment, with ZYNTEGLO.
- We currently rely on third parties to manufacture, perform quality testing, and ship our lentiviral vectors and drug products for our clinical studies and support commercialization efforts. The third parties in our supply chain are subject to restrictions in operations arising from the COVID-19 pandemic, and in addition, a number of these third parties have experienced operational disruptions, which have affected activities necessary for our research, development, and commercialization efforts. These restrictions and disruptions in operations have also given rise to staffing shortages from time to time, which may result in production slowdowns and/or disruptions in delivery systems, potentially interrupting our supply chain and limiting our ability to manufacture our lentiviral vectors and drug products for our clinical studies and for commercial use. At this time, it is unknown how long these disruptions may continue, or the full extent of their impacts.
- Health regulatory agencies globally may experience disruptions in their operations as a result of the COVID-19 pandemic. The FDA and comparable foreign regulatory agencies may have slower response times or lack resources to continue to monitor our clinical studies or to engage in other activities related to review of regulatory submissions in drug development. As a result, review, inspection, and other timelines may be materially delayed for an unknown period of time. Any de-prioritization of our clinical studies or delay in regulatory review resulting from such disruptions could materially affect the development of our product candidates. In addition, we have been engaging in reimbursement discussions with governmental health programs as part of our commercial preparation activities. It is not clear to what extent shifting priorities of the local health authorities and healthcare systems due to the COVID-19 pandemic will impact our ability to achieve market access and reimbursement for ZYNTEGLO across Europe.
- We have implemented policies at our locations to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory or manufacturing facility, a work-from-home policy applicable to the majority of our personnel, and a phased approach to bringing personnel back to our locations over time. Our increased reliance on personnel working from home may negatively impact productivity, or disrupt, delay, or otherwise adversely impact our business. In addition, this could increase our cyber security risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with local and federal regulators, ethics committees, manufacturing sites, research or clinical study sites and other important agencies and contractors. Furthermore, since the onset of the COVID-19 pandemic, our employees and contractors conducting research and development activities have been limited in the activities that they may conduct, and will continue to be subject to policies restricting access to our laboratories for an extended period of time. As a result, this could delay timely completion of preclinical activities, including completing Investigational New Drug-enabling studies or our

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ability to select future development candidates, and initiation of additional clinical trials for our development programs.

•The trading prices for our shares of common stock and other biopharmaceutical companies have been highly volatile as a result of the economic volatility and uncertainty caused by the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of shares of our common stock or such sales may be on unfavorable terms. In addition, a recession, depression or other sustained adverse market event resulting from the spread of the COVID-19 pandemic will materially and adversely affect our business, the value of our common stock, and our ability to operate under our operating plan and execute our strategy. Our business and operating plan have already been impacted by the COVID-19 pandemic, the associated governmental restrictions, and the resulting economic conditions, leading us to reduce and defer costs, adjust our priorities, timelines and expectations, and implement a revised operating plan in the first half of 2020 with the intention that it would enable us to advance our corporate strategy and pipeline during this period of uncertainty.

The extent of the impacts described above will depend on numerous evolving factors that we may not be able to accurately predict, including:

- the duration, severity, and scope of the pandemic in the United States and globally;
- the effectiveness of governmental, business and individuals' protocols and actions that have been and continue to be taken in response to the pandemic;
- the impact of the pandemic on economic activity and actions taken in response;
- the effect on patients, healthcare providers and business partners;
- demand for our products, including as a result of reduced patient visits to healthcare providers, travel restrictions, social distancing, quarantines and other containment measures;
- uncertainty as to when we will be able to resume normal clinical study enrollment and patient treatment activities, particularly at clinical study sites and qualified treatment centers located in highly impacted geographies as a result of disruptions at these sites;
- the ability to obtain or deliver sufficient and timely supplies, given the disruptions to the production capabilities of our manufacturers and suppliers, particularly with respect to the development, regulatory approval, and manufacture of COVID-19 vaccines;
- our access to the debt and equity markets on satisfactory terms, or at all;
- disruptions in regulatory oversight and actions, as a result of significant and unexpected resources expended to address the COVID-19 by regulators and industry professionals; and
- any closures of our and our partners' offices, operations and facilities.

The ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments which are difficult to predict, including the duration of the pandemic, the ultimate geographic spread of the disease, additional or modified government actions, new information that will emerge concerning the severity and impact of COVID-19 and other actions taken to contain or address its impact in the short and long term, among others. We do not yet know the full extent of potential delays or impacts on our business, our commercialization efforts, our clinical studies, our research programs, healthcare systems or the global economy, and if the ultimate impact of the COVID-19 pandemic and the resulting uncertain economic and healthcare environment is more severe than we anticipated, we may not be able to execute on our current operating plan or on our strategy. If the duration of the COVID-19 pandemic and the associated period of business and social restrictions and economic uncertainty is longer than we anticipated, our cash, cash equivalents, and marketable securities may not be sufficient to fund the activities under our operating plan for the time period that we anticipated, and we may be required to revise our operating plan further. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also have the effect of heightening many of the other risks described in this "Risk Factors" section.

**Risks related to commercialization**

*We have limited experience as a commercial company and the marketing and sale of ZYNTEGLO or future products may be unsuccessful or less successful than anticipated.*

We have limited experience as a commercial company. Consequently, there is limited information about our ability to overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical

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industry. We also have several programs in late-stage clinical development. To execute our business plan, in addition to successfully marketing and selling ZYNTEGLO and any future products, we will need to successfully:

- gain regulatory acceptance for the development and commercialization of the product candidates in our pipeline;
- obtain adequate pricing and reimbursement for ZYNTEGLO and any future products in each of the jurisdictions in which we plan to commercialize approved products;
- establish and maintain, in the geographies where we hope to treat patients, relationships with qualified treatment centers who will be treating the patients who receive ZYNTEGLO and any future products;
- manage our spending as costs and expenses increase due to clinical trials, marketing approvals, and commercialization, including for any extension of marketing approval of ZYNTEGLO, and for any future products; and
- develop and maintain successful strategic alliances.

If we are not successful in accomplishing these objectives, we may not be able to develop product candidates, commercialize ZYNTEGLO or any future products, raise capital, expand our business, or continue our operations.

*The commercial success of ZYNTEGLO, and of any future products, will depend upon the degree of market acceptance by physicians, patients, third-party payers and others in the medical community.*

The commercial success of ZYNTEGLO and of any future products will depend in part on the medical community, patients, and third-party or governmental payers accepting gene therapy products in general, and ZYNTEGLO and any future products in particular, as medically useful, cost-effective, and safe. ZYNTEGLO and any other products that we may bring to the market may not gain market acceptance by physicians, patients, third-party payers and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of ZYNTEGLO and of any future products will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the chemotherapy and myeloablative treatments associated with the procedure by which our product and any future products are administered;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- the pricing of our product and of any future products;
- publicity concerning our product, any future products, or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and payers on the benefits of our products may require significant resources and may never be successful. Our efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. Any of these factors may cause ZYNTEGLO, or any future products, to be unsuccessful or less successful than anticipated.

*If the market opportunities for our product or any future products are smaller than we believe they are, and if we are not able to successfully identify patients and achieve significant market share, our revenues may be adversely affected and our business may suffer.*

We focus our research and product development on treatments for severe genetic diseases and cancer. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product or any future products, are based on estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research, and may prove to

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be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower or more difficult to identify than expected. Additionally, the potentially addressable patient population for our product and any future products may be limited or may not be amenable to treatment with our products. For instance, in our HGB-206 clinical study of LentiGlobin for SCD, we have received notice of safety events of acute myeloid leukemia and of myelodysplastic syndrome. If these safety events are shown to be related to the use of our lentiviral vector in the manufacture of the gene therapy or the use of myeloablative regimens prior to treatment, the market opportunity for our gene therapies may be negatively impacted even if our gene therapies ultimately receive marketing approval.

Even if we obtain significant market share for a product within an approved indication, because the potential target populations for our product and for the product candidates in our pipeline are small, we may never achieve profitability without obtaining marketing approval for additional indications. For instance, we received conditional marketing approval in Europe of ZYNTEGLO for the treatment of adult and adolescent patients with TDT who do not have a  $\beta^0/\beta^0$  genotype. We do not have any assurance of whether or when ZYNTEGLO may be commercially available to pediatric patients less than 12 years of age, or to patients with all genotypes of TDT, or in markets outside of Europe. In the field of cancer, the FDA often approves new therapies initially only for use in patients with relapsed or refractory advanced disease. We expect to initially seek approval of our T cell-based product candidates in cancer in this context. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval in earlier lines of treatment and potentially as a first line therapy, but there is no guarantee that our product candidates, even if approved, would be approved for earlier lines of therapy, and, prior to any such approvals, we may have to conduct additional clinical trials. For example, BMS has submitted a BLA seeking approval from the FDA for ide-cel as a treatment for relapsed and refractory multiple myeloma. BMS is conducting the KarMMA-2, KarMMA-3, and KarMMA-4 studies with the intention to generate data to support marketing approvals for earlier lines of therapy in multiple myeloma, but there is no assurance that such studies will be successful or be sufficient.

Any of these factors may negatively affect our ability to generate revenues from sales of our product and any future products and our ability to achieve and maintain profitability and, as a consequence, our business may suffer.

*We rely on a complex supply chain for ZYNTEGLO and our product candidates. The manufacture and delivery of our lentiviral vector and drug products present significant challenges for us, and we may not be able to produce our vector and drug products at the quality, quantities, locations or timing needed to support commercialization and our clinical programs. In addition, we may encounter challenges with engaging or coordinating with qualified treatment centers needed to support commercialization.*

In order to commercialize ZYNTEGLO and any future products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We currently rely on third parties to manufacture the vector and the drug product in the commercial setting and for any clinical trials that we initiate. Currently, SAFC is the sole manufacturer of the lentiviral vector and Minaris Regenerative Medicine is the sole manufacturer of the drug product to support commercialization of ZYNTEGLO in Europe. Although we intend to eventually rely on a mix of internal and third-party manufacturers to support our commercialization efforts, we are still in the process of completing construction and qualification of our internal capacity and we have not secured commercial-scale manufacturing capacity in all of the regions where we intend to commercialize ZYNTEGLO or our late-stage product candidates, if they receive marketing approval. By building our own internal manufacturing facility, we have incurred substantial expenditures and expect to incur significant additional expenditures in the future. In addition, there are many risks inherent in the construction of a new facility that could result in delays and additional costs, including the need to obtain access to necessary equipment and third-party technology, if any. Also, we have had to, and will continue to, hire and train qualified employees to staff our manufacturing facility. We may not be able to timely or successfully build out our internal capacity or negotiate binding agreements with third-party manufacturers at commercially reasonable terms. If we fail to secure adequate capacity to manufacture our drug products or lentiviral vectors used in the manufacture of our drug products, we may be unable to execute on our development and commercialization plans on the timing that we expect.

The manufacture of our lentiviral vector and drug product is complex and requires significant expertise. Even with the relevant experience and expertise, manufacturers of cell therapy products often encounter difficulties in production, particularly in scaling out and validating initial production, managing the transition from clinical manufacturing to manufacturing in the commercial setting, and ensuring that the product meets required specifications. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot make any assurances that these problems will not occur in the future, or that we will be able to resolve or address in a timely manner or with available funds problems that occur. Because of the complexity of manufacturing our product and product candidates, transitioning production of either lentiviral vector or drug products to backup or second source manufacturing, or to internal manufacturing capacity, requires a lengthy technology transfer process and may require additional significant financial expenditures. Furthermore, our cost of goods development is at an early stage. The actual cost to manufacture our lentiviral

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vector and drug product could be greater than we expect and could materially and adversely affect the commercial viability of our product and any future products. If we or such third-party manufacturers are unable to produce the necessary quantities of lentiviral vector and our drug product, or in compliance with GMP or other pertinent regulatory requirements, and within our planned time frame and cost parameters, the development and commercialization of our product and any future products may be materially harmed. Furthermore, if we or our third-party manufacturers are unable to produce our lentiviral vectors or our drug product in quantities, in accordance with regulatory requirements, including quality requirements, or within the time frames that we need to support our development and commercialization activities, it may result in delays in our plans or increased capital expenditures.

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have agreements with suppliers. There are a small number of suppliers for certain key materials that are used to manufacture our product and product candidates. Such suppliers may not sell these key materials to us or to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these key materials by our manufacturers. Moreover, we currently do not have agreements for the commercial supply for all of these key materials.

Additionally, since the HSCs and T cells used as starting material for our drug product have a limited window of stability following procurement from a patient, we must establish transduction facilities in the regions where we wish to commercialize our product and any future products. Currently, we rely on third-party contract manufacturers in the United States and Europe to produce drug product for commercialization and for our clinical studies. Since a portion of our target patient populations will be outside the United States and Europe, we will need to establish additional transduction facilities that can replicate our transduction process in order to address those patient populations. Establishment of such facilities may be financially impractical or impeded by technical, quality, or regulatory issues related to these new sites and we may also run into technical or scientific issues related to transfer of our transduction process or other developmental issues that we may be unable to resolve in a timely manner or with available funds.

Our commercial strategy is to engage apheresis and transplant centers in our key launch regions as qualified treatment centers for the collection of patient HSCs and infusion of the drug product once manufactured. To ensure that the qualified treatment centers are prepared to collect patient HSCs and to ship them to our transduction facilities in accordance with our specifications and regulatory requirements, we train and conduct quality assessments of each center as part of engagement. These qualified treatment centers are the first and last points on our complex supply chain to reach patients in the commercial setting. We may not be able to engage qualified treatment centers in all of the regions in our commercial launch strategy, or we may encounter other challenges or delays in engaging qualified treatment centers. We may fail to manage the logistics of collecting and shipping patient material to the manufacturing site and shipping the drug product back to the patient. Logistical and shipment delays and problems caused by us, our third-party vendors, and other factors not in our control, such as weather, could prevent or delay the delivery of product to patients. If our qualified treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm. We are required to maintain a complex chain of identity and chain of custody with respect to patient material as it moves through the manufacturing process, from the qualified treatment center to the transduction facility, and back to the patient. Failure to maintain chain of identity and chain of custody could result in adverse patient outcomes, loss of product or regulatory action.

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*Although we are continuing to build out our commercial capabilities, we have no prior sales or distribution experience and limited capabilities for marketing and market access. We expect to invest significant financial and management resources to establish these capabilities and infrastructure to support commercial operations. If we are unable to establish these commercial capabilities and infrastructure or to enter into agreements with third parties to market and sell our product or any future products, we may be unable to generate sufficient revenue to sustain our business.*

Although we are continuing to build out our field team as part of our commercial launch in Europe, we have no prior sales or distribution experience and limited capabilities for marketing and market access. To successfully commercialize ZYNTEGLO and any other products that may result from our development programs, we will need to further develop these capabilities and expand our infrastructure to support commercial operations in the United States, Europe and other regions, either on our own or with others. Commercializing an autologous gene therapy such as ZYNTEGLO is resource-intensive and has required, and will continue to require, substantial investment in commercial capabilities. We are competing with companies that currently have extensive and well-funded marketing and sales operations. Without significant commercial experience as a company or the support of a third-party to perform these functions, including marketing and sales functions, we may be unable to compete successfully against these more established companies. Furthermore, a significant proportion of the patient populations for ZYNTEGLO and our potential products lies outside of the United States and Europe. We may not be able to establish our global capabilities and infrastructure in a timely manner or at all. The cost of establishing such capabilities and infrastructure may not be justifiable in light of the potential revenues generated by any particular product and/or in any specific geographic region. We currently expect to rely heavily on third parties to launch and market ZYNTEGLO and our potential products in certain geographies, if approved. We may enter into collaborations with third parties to utilize their mature marketing and distribution capabilities, but we may be unable to enter into agreements on favorable terms, if at all. If our future collaborative partners do not commit sufficient resources to commercialize ZYNTEGLO or our future products, if any, and we are unable to develop the necessary commercial and manufacturing capabilities on our own, we may be unable to generate sufficient product revenue to sustain our business.

*The insurance coverage and reimbursement status of newly-approved products is uncertain. Due to the novel nature of our technology and the potential for our product to offer lifetime therapeutic benefit in a single administration, we face additional uncertainty related to pricing and reimbursement for our product. Failure to obtain or maintain adequate coverage and reimbursement for any new or current product could limit our ability to market those products and decrease our ability to generate revenue.*

The availability and extent of reimbursement by governmental and private payers is essential for most patients to be able to afford expensive treatments, such as gene therapy products. Sales of our product and any future products will depend substantially, both domestically and abroad, on the extent to which the costs of our product and any future products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other payers. In addition, because our therapies represent new treatment approaches, the estimation of potential revenues will be complex.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, including gene therapies that are potential one-time treatments. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payers tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. A number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries. In addition, costs or difficulties with the reimbursement experienced by the initial gene therapies to receive marketing authorization may create an adverse environment for reimbursement of other gene therapies.

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these foreign jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, the revenues from sales by us or our collaborators, and the potential profitability of our product and any future products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our

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commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate or recognize from the sale of the product in that particular country. For instance, although we have received conditional marketing approval for ZYNTEGLO in the European Union and the United Kingdom, we are still in the process of negotiating pricing and reimbursement approval in the jurisdictions where we are commercializing ZYNTEGLO, and there is no assurance that the approved prices or reimbursement levels that payers will be willing to pay will be acceptable to us.

Moreover, increasing efforts by governmental and third-party payers, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product or any future products. We expect to experience pricing pressures in connection with the sale of our product and any future products, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. Net prices for drugs may be reduced by mandatory discounts or rebates required by government or private payers and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Furthermore, because our target patient populations are relatively small, the pricing and reimbursement of our product and any future products must be adequate to cover the costs to treat and support the treatment of patients. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product and any future products will be adversely affected. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

In addition, the administration of autologous drug products requires procedures for the collection of HSCs or T cells from the patient, followed by chemotherapy and myeloablative treatments, before infusion of the engineered cell therapy product. The manner and level at which reimbursement is provided for these services is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product.

We have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as ZYNTEGLO. While we are engaged in discussions with payers, there is no assurance that there will be widespread adoption of these payment models by payers. These payment models may not be sufficient for payers to grant coverage, and if we are unable to obtain adequate coverage for our product or any future products, the adoption of our product or any future products may be limited, or our ability to recognize revenue from product sales may be delayed. In addition, to the extent reimbursement for our product is subject to outcomes-based arrangements, the total payments received from product sales may vary, our cash collection of future payments and revenue assumptions from product sales will be at risk, and the timing of revenue recognition may not correspond to the timing of cash collection. We plan on commercializing our product candidates in the United States once approved, and will be subject to price reporting obligations set forth by CMS. To the extent reimbursement for our product or any future products by U.S. governmental payers is subject to outcomes-based arrangements, the increased complexity increases the risk that CMS may disagree with the assumptions and judgments that we use in our price reporting calculations, which may result in significant fines and liability.

Collectively, these factors could affect our ability to successfully commercialize our product and any future products and generate or recognize revenues, which would adversely impact our business, financial condition, results of operations and prospects.

#### Risks related to the research and development of our product candidates

*We cannot predict when or if we will obtain marketing approval to commercialize our product candidates, and the marketing approval of our product and any future products may ultimately be for more narrow indications than we expect. If our product candidates are not approved in a timely manner or at all for any reason, our business prospects, results of operations, and financial condition would be adversely affected.*

Before obtaining marketing approval from regulatory authorities for the commercialization of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity and potency, and efficacy, of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. There is a high failure rate for drugs and biologics proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical studies even after achieving promising results in earlier stage clinical studies. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

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- delays in reaching a consensus with regulatory agencies on study design;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites or due to unforeseen safety issues;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- failure to obtain sufficient cells from patients to manufacture enough drug product or achieve target cell doses;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical study sites or patients dropping out of a study;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Furthermore, the timing of our clinical studies depends on the speed at which we can recruit eligible patients to participate in testing our product candidates. The conditions for which we plan to evaluate our current product candidates in severe genetic diseases are rare disorders with limited patient pools from which to draw for clinical studies. The eligibility criteria of our clinical studies will further limit the pool of available study participants, and the process of finding and diagnosing patients may prove costly. Patients may be unwilling to participate in our studies because of negative publicity from adverse events in the biotechnology or gene therapy industries or for other reasons, including competitive clinical studies for similar patient populations. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical studies in a timely manner. We have experienced delays in some of our clinical studies in the past, and we may experience similar delays in the future.

Results from previous or ongoing studies are not necessarily predictive of our future clinical study results, and initial or interim results may not continue or be confirmed upon completion of the study. There is limited data concerning long-term safety and efficacy following treatment with our gene therapy and T cell-based product candidates. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical studies, and may not be repeated or observed in ongoing or future studies involving our product candidates. Furthermore, our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies. There can be no assurance that any of these studies will ultimately be successful or support further clinical advancement or marketing approval of our product candidates. For instance, while patients with SCD who have been treated with LentiGlobin may experience a reduction of vaso-occlusive events following successful engraftment, there can be no assurance that they will not experience vaso-occlusive events in the future. Similarly, patients with relapsed and refractory multiple myeloma who have been treated with ide-cel or the bb21217 product candidate may experience disease progression. We have experienced unexpected results in the past, and we may experience unexpected results in the future. For instance, initial results from our clinical studies of ZYNTEGLO suggested that patients with TDT who do not have a  $\beta^0/\beta^0$  genotype experienced better outcomes from treatment than patients with TDT who have a  $\beta^0/\beta^0$  genotype. Consequently, we received conditional approval in the European Union initially for the treatment of patients with TDT who do not have a  $\beta^0/\beta^0$  genotype. In order to support an application for marketing approval of ZYNTEGLO in patients with TDT who have a  $\beta^0/\beta^0$  genotype, we are conducting the HGB-212 study, but we do not know if or when ZYNTEGLO may be commercially available to all genotypes of TDT or types of  $\beta$ -thalassemia in Europe.

Even if our product candidates demonstrate safety and efficacy in clinical studies, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development. We may experience delays or rejections based upon additional government regulation from future legislation or administrative action, changes in regulatory agency policy, or additional regulatory feedback or guidance during the period of product development, clinical studies and the review process. The field of cell and gene therapy is evolving, and as more products are reviewed by regulatory authorities, regulatory authorities may impose additional requirements that were not previously anticipated. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain marketing approval for the desired age ranges, our business may suffer. Furthermore, approvals by the EMA and the European Commission may not be indicative of what the FDA may require for approval.

In general, the FDA requires the successful completion of two pivotal trials to support approval of a biologics licensing application, or BLA, but in certain circumstances, will approve a BLA based on only one pivotal trial. Because beti-cel has

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been granted the FDA's Fast Track and Breakthrough Therapy designations, we are engaged in discussions with the FDA regarding the development plans for beti-cel to enable a submission of a BLA prior to the completion of our ongoing studies. Based on these discussions, we believe the results from our ongoing Northstar-2 and Northstar-3 clinical studies, together with data from our Northstar study, the LTF-303 long-term follow up protocol, and completed HGB-205 study, could be sufficient to form the basis for a BLA submission for beti-cel to treat patients with TDT. However, it should be noted that our ability to submit and obtain approval of a BLA is ultimately an FDA review decision, which will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support the submission or approval of a BLA. Depending on the outcome of these ongoing clinical studies, the FDA may require that we conduct additional or larger pivotal trials before we can submit or obtain approval of a BLA for beti-cel for the treatment of patients with TDT. Furthermore, we are required to submit data relating to certain release assays designed to confirm the quality, purity and strength (including potency) of beti-cel as a condition for completing the BLA submission, which has the potential for further delaying the completion of our BLA submission, with the potential consequence of delaying any approval and commercial launch of beti-cel in the United States. In addition, in February 2021 we temporarily suspended marketing of ZYNTEGLO and the EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary, in light of safety events arising from our HGB-206 clinical study of LentiGlobin gene therapy for SCD. We cannot make any assurances as to what the EMA may require for ZYNTEGLO to return to the market in Europe, or what the FDA may require for approval of beti-cel in the United States.

In September 2020, we submitted a MAA to the EMA to seek approval in Europe for eli-cel for the treatment of patients with CALD. Based on our discussions with the FDA, we believe that we may be able to seek approval for eli-cel for the treatment of patients with CALD in the United States on the basis of safety and efficacy data from our ongoing Starbeam study, safety data from our ongoing ALD-104 study, and the completed ALD-103 observational study. Whether eli-cel is eligible for approval will ultimately be determined at the discretion of the FDA and EMA, and will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support approval. Depending on the outcome of our ongoing studies, the FDA in the United States and EMA and European Commission in the European Union may require that we conduct additional or larger clinical trials before eli-cel is eligible for approval.

Based on our discussions with the FDA, we believe that we may be able to seek accelerated approval for our LentiGlobin for SCD product candidate in the United States on the basis of clinical data from Group C of our ongoing HGB-206 clinical study, with our ongoing HGB-210 clinical study providing confirmatory data for full approval. We cannot be certain that data from our HGB-206 or HGB-210 clinical studies will be sufficiently robust from a safety and/or efficacy perspective to support either conditional approval or full approval. We are also engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin for SCD in Europe. Our development plan in the United States is contingent upon LentiGlobin for SCD demonstrating complete resolution of severe vaso-occlusive events, with globin response as a key secondary endpoint, and an acceptable safety profile in the study participants. Depending on the outcome of our ongoing and planned studies, the FDA may require that we conduct additional or larger clinical trials before our LentiGlobin product candidate is eligible for approval for the treatment of patients with SCD. In our discussions with FDA regarding the transition of manufacturing to the commercial setting from the clinical context, we are finalizing our plans for validating our commercial manufacturing processes and for providing the FDA with the comparability data that it requires. The FDA may not agree with these plans, or may require additional validation or comparability data as a condition for completing the BLA submission and filing. Any of these may result in delays in our ability to submit a BLA for regulatory approval of LentiGlobin for SCD. Furthermore, in light of a SUSAR of acute myeloid leukemia and a SUSAR of myelodysplastic syndrome in our HGB-206 clinical study reported to us in February 2021, the FDA has placed our clinical studies of LentiGlobin for SCD on clinical hold. We are investigating these events and plan to continue to work closely with the FDA in their review of these events, and we cannot make any assurances as to what the FDA may require to lift the clinical hold, if ever, or the timing for us to complete our investigation as to the relationship between the use of our lentiviral vector in manufacturing and these safety events. Taken together, these factors are likely to result in delays in our ability to submit a BLA for regulatory approval of LentiGlobin for SCD. In addition, we are engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin in SCD in Europe, and we cannot be certain that our HGB-206 study and HGB-210 study will be sufficient to form the basis for an initial MAA submission in Europe for the treatment of patients with SCD.

In September 2020, the FDA accepted for Priority Review the BLA submitted by BMS for ide-cel as a treatment for relapsed and refractory multiple myeloma. There is no guarantee that the FDA will conclude that the information in the BLA will be sufficient to support approval and we may fail to obtain regulatory approval in the United States for ide-cel. Additionally, certain factors beyond our and BMS' control may impact the timeliness of the regulatory reviews of our submissions or any applications for approval.

If our product candidates are ultimately not approved for any reason, our business, prospects, results of operations and financial condition would be adversely affected.

[Table of Contents](#)***Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans.***

The manufacturing processes for our lentiviral vectors and our drug products are complex. We explore improvements to our manufacturing processes on a continual basis, as we evaluate clinical and manufacturing data and based on discussions with regulatory authorities. In some circumstances, changes in the manufacturing process may require us to perform additional comparability studies, collect additional data from patients, submit additional regulatory filings, or comply with additional requirements, which may lead to delays in our clinical development and commercialization plans. For instance, following the conditional approval of ZYNTEGLO by the European Commission, we continued to refine our commercial drug product manufacturing process to narrow some of the manufacturing process parameters and to tighten the range of commercial drug product release specifications, based on an ongoing discussion with the EMA and evolving clinical data. Implementing these changes to the ZYNTEGLO commercial manufacturing process had the effect of delaying our ability to treat the first patient in the commercial context in Europe. In LentiGlobin for SCD, we plan to seek regulatory approval for drug product utilizing lentiviral vector manufactured using the scalable suspension manufacturing process, rather than the adherent manufacturing process. The FDA and EMA may not agree with our proposed plans for demonstrating the comparability of the two processes, and may require us to conduct additional studies, collect additional data, develop additional assays, or modify release specifications, which may delay our ability to submit a BLA or MAA for regulatory approval of LentiGlobin for SCD. Over time, we also intend to transition the lentiviral vector manufacturing process for ZYNTEGLO in the European Union, and beti-cel in the United States, to the suspension manufacturing process, and the timing in which we are able to make the transition will be dependent upon reaching agreement with regulatory authorities, which may require us to conduct additional studies, collect additional data, develop additional assays, or modify release specifications.

***We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product and any future products. If our competitors obtain orphan drug exclusivity for products that regulatory authorities determine constitute the same drug and treat the same indications as our product or any future products, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.***

We are engaged in the development of gene therapies for severe genetic diseases and cancer, and both fields are competitive and rapidly changing. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, more experienced manufacturing capabilities, or more established commercial infrastructure. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective, safer, or less costly than any products that we may develop, or achieve patent protection, marketing approval, product commercialization and market penetration earlier than us. Additionally, technologies developed by our competitors may render our potential products uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors. For additional information regarding our competition, see “Item 1. Business-Competition” in our Annual Report on Form 10-K.

Even if we are successful in achieving marketing approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be “highly similar,” or biosimilar, to or “interchangeable” with an FDA-approved biological product. This pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products. If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

In addition, although ZYNTEGLO and our product candidates have been granted orphan drug status by the FDA and EMA, there are limitations to the exclusivity. In the United States, the exclusivity period for orphan drugs is seven years, while pediatric exclusivity adds six months to any existing patents or exclusivity periods. In Europe, orphan drugs may be able to obtain 10 years of marketing exclusivity and up to an additional two years on the basis of qualifying pediatric studies. However,

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orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria. Additionally, a marketing authorization holder may lose its orphan exclusivity if it consents to a second orphan drug application or cannot supply enough drug. Orphan drug exclusivity also can be lost when a second applicant demonstrates its drug is “clinically superior” to the original orphan drug. Generally, if a product with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the exclusivity period for the applicable indication.

Finally, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors’ products. The availability of our competitors’ products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

***We may not be successful in our efforts to identify or discover additional product candidates.***

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform technologies, including our gene editing technology and cancer immunotherapy capabilities. Our research programs in oncology and severe genetic diseases may fail to identify other potential product candidates for clinical development for a number of reasons. We may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. If any of these events occur, we may be forced to abandon our research, development or commercialization efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

***Insertional oncogenesis is a risk of gene therapies using viral vectors. If the vectors for our product or product candidates are shown to lead to insertional oncogenesis, we may be required to halt or delay further clinical development of our product candidates, and cease the commercialization of our approved product, which may materially and negatively impact the commercial potential of our product and any future products.***

A significant risk in any gene therapy product using viral vectors is that the vector will insert in or near cancer-causing oncogenes leading to uncontrolled clonal proliferation of mature cancer cells in the patient, known as insertional oncogenesis. In published studies, lentiviral vectors have demonstrated an improved safety profile over gamma-retroviral vectors used in early gene therapy studies, which we believe is due to a number of factors including the tendency of the lentiviral vectors to integrate within genes rather than in areas that control gene expression, as well as their lack of strong viral enhancers. Notwithstanding the historical data regarding the potential safety improvements of lentiviral vectors, the risk of insertional oncogenesis remains a significant concern for gene therapy and we cannot make any assurances that it will not occur in any of our clinical studies or in the commercial setting. Insertional oncogenesis leading to leukemia or lymphoma remains a risk. For instance, clonal predominance without a known clinical correlation has been detected in some patients treated with eli-cel including vector insertions into or near genes previously associated with cancer in the general population. In February 2021, a SUSAR of acute myeloid leukemia and a SUSAR of myelodysplastic syndrome in our HGB-206 clinical study resulted in the FDA placing our clinical studies of LentiGlobin for SCD and beti-cel on clinical hold, and caused us to temporarily suspend marketing of ZYNTEGLO in the European Union. An investigation into the causes of any safety events, including these safety events, may not be conclusive or may not be definitive in eliminating the lentiviral vector as a cause. As a result, safety events such as leukemia, lymphoma, or myelodysplastic syndrome may result in delays or halt further advancement of our clinical studies, and even if a product is approved, may result in the product being removed from the market or its market opportunity being significantly reduced.

There is also the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. The FDA has stated that lentiviral vectors possess characteristics that may pose high risks of delayed adverse events. If any such adverse events occur, further advancement of our clinical studies could be halted or delayed, and we may be unable to continue to commercialize our approved product.

Furthermore, treatment with our gene therapy product and product candidates involve chemotherapy or myeloablative treatments, which can cause side effects or adverse events that are unrelated to our product and product candidates but may still impact the perception of the potential benefits of our product and any future products. For instance, myelodysplastic syndrome is a known risk of certain myeloablative regimens, and we have previously reported that in our ongoing HGB-206 study of LentiGlobin for SCD, a patient developed myelodysplastic syndrome several years after myeloablation and infusion with drug

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product, which progressed to acute myeloid leukemia, leading to the patient's death. Other patients receiving our product or product candidates may develop myelodysplastic syndrome or acute myeloid leukemia in the future, which may negatively impact the commercial prospects of our product or product candidates. Additionally, our product and any future products, or procedures associated with the administration of our product or collection of patients' cells, could potentially cause other adverse events that have not yet been predicted. The inclusion of critically ill patients in our clinical studies may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using, or the progression of their disease. Any of these events could impair our ability to commercialize our product and any future products and the commercial potential of our products will be materially and negatively impacted.

***Patients receiving T cell-based immunotherapies, such as ide-cel and the bb21217 product candidate, may experience serious adverse events, including neurotoxicity and cytokine release syndrome. If our product candidates are revealed to have high and unacceptable severity and/or prevalence of side effects or unexpected characteristics, their clinical development, marketing approval, and commercial potential will be negatively impacted, which will significantly harm our business, financial condition and prospects.***

Ide-cel and the bb21217 product candidate are chimeric antigen receptor, or CAR, T cell-based immunotherapies. In previous and ongoing clinical studies involving CAR T cell products, including those involving ide-cel and the bb21217 product candidate, patients experienced side effects such as neurotoxicity and cytokine release syndrome. There have been life-threatening events related to severe neurotoxicity and cytokine release syndrome, requiring intense medical intervention such as intubation or pressor support, and in several cases, resulted in death. Severe neurotoxicity is a condition that is currently defined clinically by cerebral edema, confusion, drowsiness, speech impairment, tremors, seizures, or other central nervous system side effects, when such side effects are serious enough to lead to intensive care. In some cases, severe neurotoxicity was thought to be associated with the use of certain lymphodepletion regimens used prior to the administration of the CAR T cell products. Cytokine release syndrome is a condition that is currently defined clinically by certain symptoms related to the release of cytokines, which can include fever, chills, low blood pressure, when such side effects are serious enough to lead to intensive care with mechanical ventilation or significant vasopressor support. The exact cause or causes of cytokine release syndrome and severe neurotoxicity in connection with treatment of CAR T cell products is not fully understood at this time. In addition, patients have experienced other adverse events in these studies, such as a reduction in the number of blood cells (in the form of neutropenia, thrombocytopenia, anemia or other cytopenias), febrile neutropenia, chemical laboratory abnormalities (including elevated liver enzymes), and renal failure.

Undesirable side effects caused by ide-cel or the bb21217 product candidate, other CAR T product candidates targeting BCMA, or our other T cell-based immunotherapy product candidates, could cause us or regulatory authorities to interrupt, delay or halt clinical studies and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or other comparable foreign regulatory authorities. In some cases, side effects such as neurotoxicity or cytokine release syndrome have resulted in clinical holds of ongoing clinical trials and/or discontinuation of the development of the product candidate. Results of our studies could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the studies or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from T cell-based immunotherapies are not normally encountered in the general patient population and by medical personnel. Medical personnel may need additional training regarding T cell-based immunotherapy product candidates to understand their side effects. Inadequate training in recognizing or failure to effectively manage the potential side effects of T cell-based immunotherapy product candidates could result in patient deaths. Any of these occurrences may harm our business, financial condition and prospects significantly.

***Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product and any future products or adversely affect our ability to conduct our business or obtain and maintain marketing approvals for our product and product candidates.***

Public perception may be influenced by claims that gene therapy, including gene editing technologies, is unsafe or unethical, and research activities and adverse events in the field, even if not ultimately attributable to us or our product or product candidates, could result in increased governmental regulation, unfavorable public perception, challenges in recruiting patients to participate in our clinical studies, potential regulatory delays in the testing or approval of our potential products, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any approved products.

#### Risks related to our reliance on third parties

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***We are dependent on BMS for the successful development and commercialization of ide-cel and bb21217. If BMS does not devote sufficient resources to the development of ide-cel and bb21217, is unsuccessful in its efforts, or chooses to terminate its agreements with us, our business will be materially harmed.***

We are co-developing and co-promoting ide-cel in the United States with BMS under our amended and restated co-development and co-promotion agreement with BMS, or the Ide-cel CCPS. Under the Ide-cel CCPS, we and BMS share the obligation to develop and commercialize ide-cel in the United States. In addition, we have exclusively licensed to BMS the right to develop and commercialize the bb21217 product candidate, and we retain an option to co-develop and co-promote bb21217 in the United States under our license agreement with BMS. With respect to bb21217, we are responsible for completing the ongoing CRB-402 study, but BMS is responsible for further clinical development and commercialization costs, unless we choose to exercise our option to co-develop and co-promote bb21217 in the United States. If we exercise our option to co-develop and co-promote bb21217 in the United States, we and BMS will share the obligation to develop and commercialize bb21217 in the United States.

In our partnership with BMS, BMS is obligated to use commercially reasonable efforts to develop and commercialize ide-cel and bb21217. BMS may determine however, that it is commercially reasonable to de-prioritize or discontinue the development of ide-cel and bb21217. These decisions may occur for many reasons, including internal business reasons (including due to the existence of other BMS programs that are potentially competitive with ide-cel and bb21217), results from clinical trials or because of unfavorable regulatory feedback. Further, on review of the safety and efficacy data, the FDA may impose requirements on one or both of the programs that render them commercially nonviable. In addition, under our agreements with BMS, BMS has certain decision-making rights in determining the development and commercialization plans and activities for the programs. We may disagree with BMS about the development strategy it employs, but we will have limited rights to impose our development strategy on BMS. Similarly, BMS may decide to seek marketing approval for, and limit commercialization of, ide-cel or bb21217 to narrower indications than we would pursue. More broadly, if BMS elects to discontinue the development of ide-cel or bb21217, we may be unable to advance the product candidate ourselves.

This partnership may not be scientifically or commercially successful for us due to a number of important factors, including the following:

- BMS has wide discretion in determining the efforts and resources that it will apply to its partnership with us. The timing and amount of any development milestones, and downstream commercial profits, milestones and royalties that we may receive under such partnership will depend on, among other things, BMS's efforts, allocation of resources and successful development and commercialization of ide-cel, bb21217 and other product candidates that are the subject of its collaboration with us.
- BMS may develop and commercialize, either alone or with others, products that are similar to or competitive with ide-cel, bb21217 and other product candidates that are the subject of its collaboration with us. For example, BMS is currently commercializing a number of its existing products, including lenalidomide and pomalidomide, for certain patients with relapsed and refractory multiple myeloma and is also developing orvacabtagene autoleucel, another CAR-T product candidate targeting BCMA that it obtained through its acquisition of Juno Therapeutics, Inc. in March 2018.
- BMS may terminate its partnership with us without cause and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities.
- BMS may develop or commercialize our product candidates in such a way as to elicit litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability.
- BMS may not comply with all applicable regulatory requirements, or may fail to report safety data in accordance with all applicable regulatory requirements.
- If BMS were to breach its arrangements with us, we may need to enforce our right to terminate the agreement in legal proceedings, which could be costly and cause delay in our ability to receive rights back to the relevant product candidates. If we were to terminate an agreement with BMS due to BMS's breach or BMS terminated the agreement without cause, the development and commercialization of ide-cel or bb21217 product candidates that are the subject of its collaboration with us could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue development and commercialization of these product candidates on our own if we choose not to, or are unable to, enter into a new collaboration for these product candidates.

BMS may enter into one or more transactions with third parties, including a merger, consolidation, reorganization, sale of substantial assets, sale of substantial stock or other change in control, which could divert the attention of its management and adversely affect BMS's ability to retain and motivate key personnel who are important to the continued development of the programs under the strategic partnership with us. In addition, the third-party to any such transaction could determine to re-

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prioritize BMS's development programs such that BMS ceases to diligently pursue the development of our programs and/or cause the respective collaboration with us to terminate.

***We rely on third parties to conduct some or all aspects of our lentiviral vector production, drug product manufacturing, and testing, and these third parties may not perform satisfactorily.***

We do not independently conduct all aspects of our lentiviral vector production, drug product manufacturing, and testing. We currently rely, and expect to continue to rely, on third parties with respect to these items, including manufacturing and testing in the commercial context.

Our reliance on these third parties for manufacturing, testing, research and development activities reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for products that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical studies are conducted in accordance with the study plan and protocols, and that our lentiviral vectors and drug products are manufactured in accordance with GMP as applied in the relevant jurisdictions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines, conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, or manufacture our lentiviral vectors and drug products in accordance with GMP, whether due to the impacts of COVID-19 or otherwise, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies and manufacturing process validation activities required to support future IND, MAA and BLA submissions and approval of our product candidates, or to support commercialization of our products, if approved. Many of our agreements with these third parties contain termination provisions that allow these third parties to terminate their relationships with us at any time. If we need to enter into alternative arrangements, our product development and commercialization activities could be delayed.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the products ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- the risk that these activities are not conducted in accordance with our study plans and protocols;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

We may be forced to manufacture lentiviral vector and drug product ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our lentiviral vector or drug product candidates may be unique or proprietary to the original manufacturer, and we may have difficulty or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. Any of these events could lead to clinical study delays or failure to obtain marketing approval, or impact our ability to successfully commercialize our product or any future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

***We and our contract manufacturers are subject to significant regulation with respect to manufacturing our product and product candidates. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.***

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product and product candidates, are subject to extensive regulation. Some components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product and product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA or MAA on a timely basis and where required, must adhere to the FDA's or other regulator's good laboratory practices, or GLP, and GMP regulations enforced by the FDA or other regulator through facilities inspection programs. Some of our contract

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manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA or other marketing approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of marketing approval of our product and potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other marketing approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third-party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other regulators can impose regulatory sanctions including, among other things, refusal to approve a pending application for a biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. The number of manufacturers with the necessary manufacturing capabilities is limited. In addition, an alternative manufacturer would need to be qualified through a BLA supplement or similar regulatory submission which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our product and any future products, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenues.

***We expect to rely on third parties to conduct, supervise and monitor our clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.***

We expect to rely on CROs and clinical study sites to ensure our clinical studies are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's and other regulatory authorities' GCPs for conducting, recording and reporting the results of clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical studies may be deemed unreliable and the FDA and other regulatory authorities may require us to perform additional clinical studies before approving any marketing applications.

If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical studies may be extended, delayed or terminated, and we may not be able to obtain marketing approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

***Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.***

Because we rely on third parties to manufacture our vectors and our drug products, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy platform, we must, at times, share trade

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secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

#### **Risks related to our financial condition and capital requirements**

***We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.***

We have incurred net losses in each year since our inception in 1992, including net losses of \$618.7 million for the year ended December 31, 2020. As of December 31, 2020, we had an accumulated deficit of \$2.90 billion. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to generate revenues. We have devoted significant financial resources to research and development, including our clinical and preclinical development activities, which we expect to continue for the foreseeable future. To date, we have financed our operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. We do not expect to generate any product revenues until we recognize revenue from the sale of ZYNTEGLO in the European Union for the treatment of adult and adolescent patients with TDT who do not have a  $\beta^0/\beta^0$  genotype, and we do not expect to generate meaningful product revenues until our conditional marketing approval for ZYNTEGLO is renewed. Following marketing approval, our future revenues will depend upon the size of any markets in which our product and any future products have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payers and adequate market share for our product and any future products in those markets.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and preclinical and clinical development of our product candidates, including ide-cel, which we are co-developing with BMS;
- establish capabilities to support our commercialization efforts, including establishing a sales, marketing and distribution infrastructure in the United States and Europe, and to commercialize ZYNTEGLO and any other products for which we may obtain marketing approval;
- obtain, build and expand manufacturing capacity, including capacity at third-party manufacturers and our own manufacturing facility;
- initiate additional research, preclinical, clinical or other programs as we seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel; and
- experience any delays or encounter issues with any of the above.

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The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

***We have never generated any revenue from product sales and may never be profitable.***

Our ability to generate revenues and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory, pricing and reimbursement approvals necessary to commercialize our product and any future products. Our ability to generate revenues from product sales depends heavily on our success in:

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable, commercial-scale, reproducible, and transferable manufacturing process for our vectors and drug products;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development for our product candidates and commercial demand for any approved product;
- launching and commercializing any approved product, either by collaborating with a partner or, if launched independently, by establishing a field-based team, marketing and distribution infrastructure;
- obtaining sufficient pricing and reimbursement for any approved product from private and governmental payers;
- obtaining market acceptance and adoption of any approved product and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; and
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how.

We expect to continue to incur significant expenditures for the foreseeable future, and we expect these expenditures to increase as we commercialize ZYNTEGLO in the European Union, which costs may increase with any increased competition. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate product revenues, we may not become profitable and may need to obtain additional funding to continue operations.

***From time to time, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.***

We are currently advancing our programs in β-thalassemia, SCD, CALD, and multiple myeloma through clinical development and other product candidates through preclinical development. Developing and commercializing gene therapy products is expensive, and we expect our research and development expenses and our commercialization expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates and progress our commercialization efforts.

As of December 31, 2020, our cash, cash equivalents and marketable securities were \$1.27 billion. In response to the ongoing COVID-19 pandemic and the associated economic conditions, we revised our operating plan to execute on our strategy during this period of uncertainty. Based on our current business plan, we expect our cash, cash equivalents and marketable securities will be sufficient to fund planned operations for at least the next twelve months from the date of issuance of these financial statements. Our current business plan assumes continued rigorous prioritization and focus on our expenses, real estate optimization, and exploration of additional sources of funding to further strengthen our financial position. However, our operating plan may change further as a result of the COVID-19 pandemic and the surrounding economic conditions, as well as many other factors currently unknown to us. In addition, we may seek additional funds through public or private equity or debt

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financings, government or other third-party funding, marketing and distribution arrangements or other collaborations, strategic alliances and licensing arrangements or a combination of these approaches, during this period. In any event, we will require additional capital to obtain marketing approval for, and to commercialize, our product candidates. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic objectives.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our approved product and product candidates. In addition, we cannot guarantee that financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, or if revenues from collaboration arrangements or product sales are less than we have projected, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

***If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements are incorrect, our actual results may vary from those reflected in our projections and accruals.***

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. We may be incorrect in our assumptions regarding the applicability of drug pricing programs and rebates that may be applicable to our product or any future products, which may result in our under- or over-estimating our anticipated product revenues especially as applicable laws and regulations governing pricing evolve over time. In addition, to the extent payment for our product or any future products is subject to outcomes-based arrangements over time, the total payments received from product sales may vary, our cash collection of future payments and revenue assumptions from product sales will be at risk, and the timing of revenue recognition may not correspond to the timing of cash collection.

Further, from time to time we issue financial guidance relating to our expectations for our cash, cash equivalents, and marketable securities available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

***Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.***

Our operating results are difficult to predict and will likely fluctuate from quarter to quarter and year to year. As we begin to generate product sales of ZYNTEGLO in Europe, we expect that our product sales will be difficult to predict from period to period, given the absence of historical sales data. This uncertainty is heightened by the unpredictable scope of the impact of the COVID-19 pandemic, which has adversely affected the operations of third parties upon which we rely in our commercialization efforts, patient access to hospitals, physicians' offices, clinics and other administration sites, and global economic conditions, as well as caused a re-prioritization of healthcare services.

In addition, we have entered into licensing and collaboration agreements with other companies that include research and development funding and milestone payments to us, and we expect that amounts earned from our collaboration agreements will continue to be an important source of our revenues. Accordingly, our revenues will also depend on research and development funding and the achievement of development and clinical milestones under our existing collaboration and license agreements, including, in particular, our collaborations with BMS and Regeneron, as well as entering into potential new collaboration and

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license agreements. These payments may vary significantly from quarter to quarter and any such variance could cause a significant fluctuation in our operating results from one quarter to the next.

Further, changes in our operations, such as increased development, manufacturing and clinical trial expenses in connection with our expanding pipeline programs, or our undertaking of additional programs, or business activities, or entry into strategic transactions, including potential future acquisitions of products, technologies or businesses may also cause significant fluctuations in our expenses.

The cumulative effects of these factors, further exacerbated by the impacts of the ongoing COVID-19 pandemic on healthcare systems and economic conditions, will likely result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

#### **Risks related to our business operations**

*We are commercializing ZYNTEGLO outside of the United States, and therefore we will be subject to the risks of doing business outside of the United States.*

Because we are commercializing ZYNTEGLO outside of the United States, our business is subject to risks associated with doing business outside of the United States. Accordingly, our business and financial results in the future could be adversely affected due to a variety of factors, including:

- efforts to develop an international commercial and supply chain organization may increase our expenses, divert our management's attention from the acquisition or development of product candidates or cause us to forgo profitable licensing opportunities in these geographies;
- requirements or limitations imposed by a specific country or region on potential qualified treatment centers or other aspects of commercialization applicable to autologous gene therapies such as ours;
- changes in a specific country's or region's political and cultural climate or economic condition, including as a result of the COVID-19 pandemic;
- unexpected changes in foreign laws and regulatory requirements;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- inadequate intellectual property protection in foreign countries;
- trade-protection measures, import or export licensing requirements such as Export Administration Regulations promulgated by the U.S. Department of Commerce and fines, penalties or suspension or revocation of export privileges;
- the effects of applicable foreign tax structures and potentially adverse tax consequences; and
- significant adverse changes in foreign currency exchange rates, including as a result of the United Kingdom's exit from the European Union, or Brexit.

In addition to FDA and related regulatory requirements in the United States and abroad, we are subject to extensive additional federal, state and foreign anti-bribery regulation, which include the U.S. Foreign Corrupt Practices Act, the U.K. Bribery Act, and similar laws in other countries outside of the United States. We have developed and implemented a corporate compliance program based on what we believe are current best practices in the pharmaceutical industry for companies similar to ours, but we cannot guarantee that we, our employees, our consultants or our third-party contractors are or will be in compliance with all federal, state and foreign regulations regarding bribery and corruption. Moreover, our partners and third-party contractors located outside the United States may have inadequate compliance programs or may fail to respect the laws and guidance of the territories in which they operate. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could also have an adverse effect on our business, financial condition and results of operations.

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*As we evolve from a U.S.-based company primarily involved in discovery, preclinical research and clinical development into a company that develops and commercializes multiple drugs with an international presence, we will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.*

We received conditional marketing authorization for our first product in 2019 and have launched ZYNTEGLO in Europe, which we hope will be the first of a sequence of marketing approvals and commercial launches for multiple products across multiple geographies. As we advance multiple product candidates through late-stage clinical research and plan submissions for marketing authorizations, we are expanding our operations in the United States and Europe. As of December 31, 2020, we had 1,201 full-time employees. As we pursue our development and commercialization strategy, we expect to expand our full-time employee base and to hire more consultants and contractors in the United States and Europe. This expected growth may place a strain on our administrative and operational infrastructure. As a result, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Recruiting and retaining qualified employees, consultants and advisors for our business, including scientific and technical personnel, will be critical to our success. Competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees.

***Even if we receive marketing approval for a product candidate, any approved product will remain subject to regulatory scrutiny.***

Even if we obtain marketing approval in a jurisdiction, regulatory authorities may still impose significant restrictions on the indicated uses or marketing of any approved products such as ZYNTEGLO, or impose ongoing requirements for potentially costly post-approval studies, post-market surveillance or patient or drug restrictions. For example, the FDA typically advises that patients treated with gene therapy undergo follow-up observations for potential adverse events for a 15-year period. In February 2021, we temporarily suspended marketing of ZYNTEGLO and the EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary. Additionally, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices, or GMP, and adherence to commitments made in the BLA. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following marketing approval for a product, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical studies;
- refuse to approve a pending marketing application, such as a BLA or supplements to a BLA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

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Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any approved product and generate revenues.

***We are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties, reputational harm, and diminished profits and future earnings.***

In the United States, the research, manufacturing, distribution, sale, and promotion of drugs and biologic products are subject to regulation by various federal, state, and local authorities in addition to FDA, including CMS, other divisions of the HHS, (e.g., the Office of Inspector General), the United States Department of Justice offices of the United States Attorney, the Federal Trade Commission and state and local governments. Our operations are directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations described in more detail under "*Item 1. Business--Government regulation*" in our Annual Report. These include the federal Anti-Kickback Statute, federal civil and criminal false claims laws and civil monetary penalty laws (including False Claims Laws), HIPAA, transparency requirements created under the Affordable Care Act, as well as analogous state and foreign laws.

These laws apply to, among other things, our sales, marketing and educational programs. State and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. Most recently, the Bipartisan Budget Act of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute. Enforcement agencies also continue to pursue novel theories of liability under these laws. In particular, government agencies have recently increased regulatory scrutiny and enforcement activity with respect to programs supported or sponsored by pharmaceutical companies, including reimbursement and co-pay support, funding of independent charitable foundations and other programs that offer benefits for patients. Several investigations into these programs have resulted in significant civil and criminal settlements.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, imposes requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition to HIPAA, as amended by HITECH, and their respective implementing regulations, California recently enacted the California Consumer Privacy Act, or CCPA, which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA will require covered companies to provide certain disclosures to consumers about its data collection, use and sharing practices, and to provide affected California residents with ways to opt-out of certain sales or transfers of personal information. The CCPA went into effect on January 1, 2020, and the California Attorney General will commence enforcement actions against violators beginning July 1, 2020. While there is currently an exception for protected health information that is subject to HIPAA, as currently written, the CCPA may impact our business activities. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

In the European Union, interactions between pharmaceutical companies, healthcare professionals, and patients are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct in the individual EU member states. The provision of benefits or advantages to healthcare professionals to induce or encourage the

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prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the European Union. Also, direct-to-consumer advertising of prescription-only medicinal products is prohibited at the European Union level and in the individual member states. In addition, the UK Bribery Act applies to any company incorporated in or “carrying on business” in the UK, irrespective of where in the world the alleged bribery activity occurs, which could have implications for our interactions with physicians both in and outside of the UK. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union member states must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician’s employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union member states. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the European Union member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

EU member states, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the European Union, the collection and use of personal health data is currently governed by the provisions of the General Data Protection Regulation, or the GDPR. The GDPR, together with the national legislation of the individual EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals for the consent to be considered valid, the transfer of personal data out of the European Economic Area, security breach notifications, the use of third-party processors in connection with the processing of the personal data, confidentiality of the personal data, as well as substantial potential fines for breaches of the data protection obligations. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the European Union. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR. Further, Brexit has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated.

*We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our approved product or product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our approved product or product candidates, our marketing approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.*

The use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients participating in clinical trials, consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our product or product candidates. There is a risk that our product or product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical study participants;
- costs due to related litigation;
- distraction of management’s attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to develop our product candidates or commercialize any approved product; and
- decreased demand for any approved product.

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We carry product liability insurance and we believe our product liability insurance coverage is sufficient in light of our current clinical programs and approved product; however, we may not be able to maintain insurance coverage at commercially reasonable cost or in sufficient amounts to protect us against losses due to liability. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our approved product and product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our approved product or product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain marketing approval for any approved product, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our marketing approval process in other countries, or impact and limit the type of marketing approval our product candidates may receive or any approved product maintains. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

***Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.***

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the Affordable Care Act, was passed, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, expanded the types of entities eligible for the 340B drug discount program, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (increased pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the Affordable Care Act in the future. Various portions of the Affordable Care Act are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court. It is unclear whether the Affordable Care Act will be overturned, repealed, replaced, or further amended. We cannot predict what effect further changes to the Affordable Care Act would have on our business.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2025 unless Congress takes additional action. These reductions were extended through 2029 through subsequent legislative amendments. In January 2013, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation

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designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal years 2019 and 2020 contain further drug price control measures that could be enacted during the budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private third-party payers.

The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize ZYNTEGLO and any other products for which we obtain marketing approval.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

*Our computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates' development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.*

Our computer systems and those of our current or future third-party collaborators, service providers, contractors and consultants may fail and are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, service providers, contractors and consultants, and the large amounts of information stored on those systems make those systems vulnerable to service interruptions, security breaches, or other failures, resulting from inadvertent or intentional actions by our employees or those of third-party business partners, or from cyber-attacks by malicious third parties. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized groups and individuals with a wide range of motives and expertise. In addition to extracting sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The prevalent use of mobile devices also increases the risk of data security incidents. If we experience a material system failure, accident or security breach that causes interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in significant reputational, financial, legal, regulatory, business or operational harm. For example, the loss of clinical trial data for our product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. In addition, we rely on third-party service providers for management of the manufacture and delivery of drug product to patients in the commercial context, including for chain of identity and chain of custody. We also rely on third-party service providers for aspects of our internal control over financial reporting and such service providers may experience a material system failure or fail to carry out their obligations in other respects, which may impact our ability to produce accurate and timely financial statements, thus harming our operating results, our ability to operate our business, and our investors' view of us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to material failures, security breaches, cyberattacks and other related breaches.

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Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations to third parties, or any data security incidents or other security breaches that result in the unauthorized access, release or transfer of sensitive information, including personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us. These events could cause third parties to lose trust in us or could result in claims by third parties asserting that we have breached our privacy, confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents.

**Risks related to the proposed separation of our business**

*The proposed separation of our business into two independent, publicly traded companies is subject to various risks and uncertainties and may not be completed on the terms or timeline currently contemplated, if at all, and will involve significant time, effort and expense, which could harm our business, results of operations and financial condition.*

In January 2021, we announced our intent to separate our oncology programs from our severe genetic disease programs, resulting in two independent, publicly traded companies, bluebird bio and a new company, or Oncology NewCo. Following the separation, bluebird bio is expected to focus on the development and commercialization of therapies in β-thalassemia, cerebral adrenoleukodystrophy and sickle cell disease in the United States and Europe. Oncology NewCo is expected to focus on the investigational BCMA directed CAR T cell therapy, ide-cel, in multiple myeloma and continued development of investigational bb21217 product candidate, as well as research and development efforts in our oncology pipeline.

The separation is expected to be completed by the end of 2021, subject to receipt of a favorable IRS ruling and the satisfaction of certain conditions. Unexpected developments, including adverse market conditions or tax consequences or delays or difficulties effecting the proposed separation, could delay, prevent or otherwise adversely impact the anticipated benefits from the proposed separation. Consummation of the separation also will require final approval from our board of directors. We may not complete the separation on the terms or on the timeline that we announced, or may, for any or no reason and at any time until the proposed separation is complete, abandon the separation or modify or change its terms. Any of the foregoing may result in our not achieving the operational, financial, strategic and other benefits we anticipate realizing as a result of the separation, and in each case, our business, results of operations and financial condition could be adversely affected.

We will incur significant expenses in connection with the proposed separation, and such costs and expenses may be greater than we anticipate. In addition, completion of the separation will require a significant amount of management time and effort, which may disrupt our business or otherwise divert management's attention from other aspects of our business, including strategic initiatives, discovery, development and commercialization efforts and relationships with our partners and other third parties. Any of the foregoing could adversely affect our business, results of operations and financial condition.

***We may fail to realize some or all of the anticipated benefits of the proposed separation.***

Even if the separation is completed, the anticipated operational, financial, strategic and other benefits of the separation may not be achieved. The combined value of the common stock of the two publicly-traded companies may not be equal to or greater than what the value of our common stock would have been had the separation not occurred. The combined value of the common stock of the two companies could be lower than anticipated for a variety of reasons, including the failure of either company to operate and compete effectively as an independent company. The common stock price of each company may experience periods of extreme volatility. In addition, the two independent companies will be smaller and less diversified, with a narrower business focus, and may be more vulnerable to changing market conditions. The separation also presents a number of significant risks to our internal processes, including the failure to maintain an adequate control environment due to changes to our infrastructure technology systems and financial reporting processes.

*If the distribution of shares of the Oncology Newco, together with certain related transactions, does not qualify as a transaction that is generally tax-free for U.S. federal income tax purposes, our stockholders and we could be subject to significant tax liabilities.*

In connection with the distribution of shares in of Oncology Newco, we may seek a private letter ruling from the IRS (the "IRS Ruling") and an opinion from our tax advisor (the "Tax Opinion") to the effect that, among other things, the distribution of shares in Oncology Newco, together with certain related transactions, will generally qualify as tax-free for U.S. federal income tax purposes under Sections 368(a)(1)(D) and 355 of the U.S. Internal Revenue Code of 1986, as amended (the "Code"). The IRS Ruling and the Tax Opinion will rely on certain facts, assumptions, representations, and undertakings from us and Oncology Newco, including those regarding the past and future conduct of the companies' respective businesses and other matters. Notwithstanding the IRS Ruling and the Tax Opinion, the IRS could determine that the distribution or any such related

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transaction is taxable if it determines that any of these facts, assumptions, representations or undertakings are not correct or have been violated, or that the distribution should be taxable for other reasons, including if the IRS were to disagree with the conclusions in the Tax Opinion. The Tax Opinion will not be binding on the IRS or the courts. Accordingly, the IRS or the courts may challenge the conclusions stated in the Tax Opinion and such challenge could prevail.

If the distribution were determined to be taxable for U.S. federal income tax purposes, our stockholders that receive shares of Oncology Newco in the distribution would be treated as having received a distribution of property in an amount equal to the fair value of such Oncology Newco shares on the distribution date and could incur significant income tax liabilities. Such distribution would be taxable to our stockholders as a dividend to the extent of our current and accumulated earnings and profits. Any amount that exceeded our current and accumulated earnings and profits would be treated first as a non-taxable return of capital to the extent of the relevant stockholder's tax basis in its shares of stock, with any remaining amount being taxed as capital gain. We would recognize a taxable gain in an amount equal to the excess, if any, of the fair market value of the shares of Oncology Newco common stock held by us on the distribution date over our tax basis in such shares.

#### **Risks related to our intellectual property**

*If we are unable to obtain or protect intellectual property rights related to our product candidates, we may not be able to compete effectively in our markets.*

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. Several patent applications covering our product candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third-party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, and information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our

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trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

***Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.***

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, *ex parte* reexaminations, post-grant review, and *inter partes* review proceedings before the U.S. Patent and Trademark Office, or U.S. PTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

***We may not be successful in obtaining or maintaining necessary rights to gene therapy product components and processes for our development pipeline through acquisitions and in-licenses.***

Presently we have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates and commercialize our approved product. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights.

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that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

For example, we sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

***If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.***

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance the development of our product candidates or allow commercialization of our approved product, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates, approved product, or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In many cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected approved product or product candidates.

[Table of Contents](#)***We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.***

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including patent eligible subject matter, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our approved product and/or product candidates. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

***We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.***

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

***We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.***

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We have had in the past, and we may also have in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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***Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.***

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

***Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

***We may not be able to protect our intellectual property rights throughout the world.***

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

**Risks related to ownership of our common stock**

***The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchase them.***

Companies trading in the stock market in general, and The NASDAQ Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and biotechnology and pharmaceutical industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

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The market price of our common stock has been volatile in the past, and may continue to be volatile for the foreseeable future. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical or clinical studies;
- reports of adverse events in our product, product candidates or other gene therapy products, or in clinical studies of such products;
- inability to obtain additional funding;
- any delay in filing an IND, MAA or BLA for any of our product candidates, and any adverse development or perceived adverse development with respect to the regulatory authority's review of that IND, MAA or BLA;
- failure to successfully manage the commercial launch of ZYNTEGLO, or our product candidates following marketing approval, including failure to manage our supply chain operations in the coordination and delivery of drug product to patients at qualified treatment centers;
- failure to obtain sufficient pricing and reimbursement for ZYNTEGLO or our product candidates from private and governmental payers;
- failure to obtain market acceptance and adoption of ZYNTEGLO or any other potential product following marketing approval;
- developments concerning the proposed separation of our programs into two independent, publicly-traded companies;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for ZYNTEGLO or our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

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***Actual or potential sales of our common stock by our employees, including our executive officers, pursuant to pre-arranged stock trading plans could cause our stock price to fall or prevent it from increasing for numerous reasons, and actual or potential sales by such persons could be viewed negatively by other investors.***

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers and members of our board of directors, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing for numerous reasons.

***Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.***

Additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2013 Stock Option and Incentive Plan, or the 2013 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2013 Plan automatically increases each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2013 Plan each year. If our board of directors or compensation committee elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall. We also have an Employee Stock Purchase Plan and any shares of common stock purchased pursuant to that plan will also cause dilution.

***We are subject to securities class action litigation, which may result in substantial costs and a diversion of management's attention and resources, which could harm our business.***

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities, and on February 12, 2021, a class action complaint was filed in the United States District Court for the Eastern District of New York, *Leung v. bluebird bio, Inc., et. al.*, Case No. 1:21-cv-00777, by a purported stockholder against us and certain of our officers, and we may face additional securities class action litigation in the future. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years, and we expect to experience continued stock price volatility. Defending against the current litigation and any future litigation could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

***Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.***

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We have completed several financings since our inception and prior to our initial public offering in 2013, which we believe have resulted in a change in control as defined by IRC Section 382. We completed a study through September 2019 confirming no ownership changes have occurred since our initial public offering in 2013. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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***We do not intend to pay cash dividends on our common stock so any returns will be limited to the value of our stock.***

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

***Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.***

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

***Changes in tax law could adversely affect our business and financial condition.***

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, on March 27, 2020, President Trump signed into law the “Coronavirus Aid, Relief, and Economic Security Act” or the CARES Act, which included certain changes in tax law intended to stimulate the U.S. economy in light of the COVID-19 pandemic, including temporary beneficial changes to the treatment of net operating losses, interest deductibility limitations and payroll tax matters. On December 27, 2020, President Trump signed into law the “Consolidated Appropriations Act”, which included additional stimulus relief for the COVID-19 pandemic in the form of modifications to the refundable employee retention credit under the CARES Act and credit extenders, and spending bill for the 2021 fiscal year. Future changes in tax laws could have a material adverse effect on our

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business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

**Item 1B. Unresolved Staff Comments**

Not applicable.

**Item 2. Properties**

Below is a summary of our material owned and leased properties as of December 31, 2020:

***Massachusetts***

Our corporate headquarters encompasses approximately 253,108 square feet of office and laboratory space and is located at 60 Binney Street, Cambridge, Massachusetts. The lease commenced on October 1, 2016 and will continue until March 31, 2027. We have the option to extend the 60 Binney Street lease for two successive five-year terms.

In April 2019, we entered into a sublease agreement for approximately 267,278 square feet of office space located at 50 Binney Street, Cambridge, Massachusetts. The lease will commence when the space is available for use, which is anticipated to be in the first half of 2022, and is expected to terminate on December 31, 2030.

***Washington***

We lease office and laboratory space in Seattle, Washington, totaling approximately 58,314 square feet. The lease commenced on January 1, 2019 and will continue through April 2028. We have the option to extend the lease for one five-year term.

***North Carolina***

In November 2017, we purchased a 125,000 square foot manufacturing facility located in Durham, North Carolina to provide manufacturing capacity for lentiviral vector in support of our current and planned gene and cell therapies.

***Switzerland***

Our European headquarters encompasses 1,136 square meters of office space and is located in Zug, Switzerland. The lease for our European headquarters commenced on January 1, 2019 and will continue for 60 months with the option to renew for 2 successive 60 month terms.

We believe that our existing facilities are adequate for our current needs.

**Item 3. Legal Proceedings**

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements, employment and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of December 31, 2020, we were not party to any legal or arbitration proceedings that may have, or have had in the recent past, significant effects on our financial position or profitability. We believe no governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

On February 12, 2021, a class action complaint was filed in the United States District Court for the Eastern District of New York, *Leung v. bluebird bio, Inc., et. al.*, Case No. 1:21-cv-00777, by a purported stockholder against us and certain of our officers. The complaint alleges violations of Section 10(b) of the Securities Exchange Act and Rule 10b-5 promulgated thereunder against all defendants and violations of Section 20(a) of the Exchange Act against the officers and seeks unspecified damages. The allegations relate to our disclosure on November 4, 2020 that we were adjusting the expected timing of submission of a BLA to the FDA for LentiGlobin for sickle cell disease to late 2022.

**Item 4. Mine Safety Disclosures**

Not applicable.

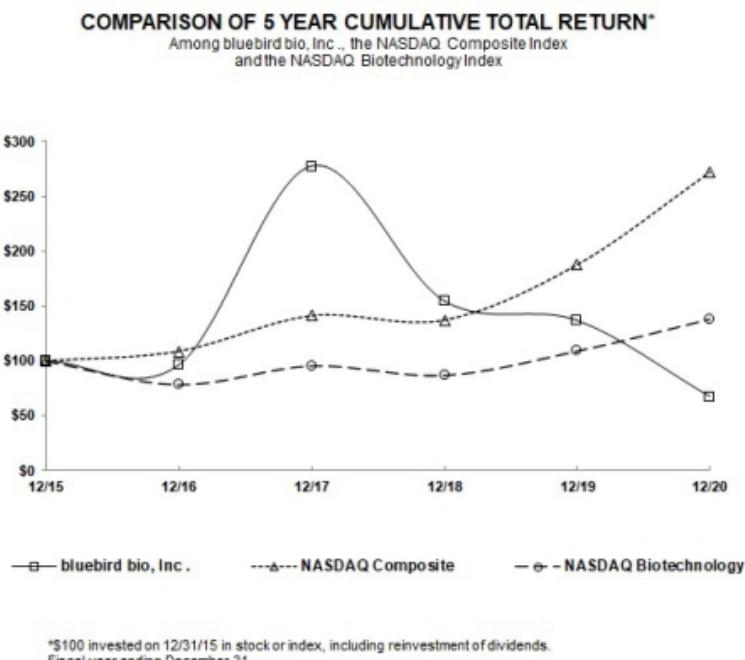
[Table of Contents](#)**PART II****Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities**

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE." On February 18, 2021, the last reported sale price for our common stock on the Nasdaq Global Select Market was \$26.95 per share.

**Stock Performance Graph**

The graph set forth below compares the cumulative total stockholder return on our common stock between December 31, 2015 and December 31, 2020, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of \$100 on December 31, 2015 of our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.

**Holders**

As of February 18, 2021, there were approximately 9 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

**Dividends**

We have not paid any cash dividends on our common stock since inception and do not anticipate paying cash dividends in the foreseeable future.

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**Securities Authorized for Issuance Under Equity Compensation Plans**

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

**Item 6. Reserved**

[Table of Contents](#)**Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations**

*The following information should be read in conjunction with the consolidated financial statements and related notes thereto included in this Annual Report on Form 10-K.*

*In addition to historical information, this report contains forward-looking statements that involve risks and uncertainties which may cause our actual results to differ materially from plans and results discussed in forward-looking statements. We encourage you to review the risks and uncertainties discussed in the sections entitled Item 1A, "Risk Factors" and "Forward-Looking Statements" included at the beginning of this Annual Report on Form 10-K. The risks and uncertainties can cause actual results to differ significantly from those forecast in forward-looking statements or implied in historical results and trends.*

*We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.*

**Overview**

We are a biotechnology company committed to researching, developing, and commercializing potentially transformative gene therapies for severe genetic diseases and cancer. We have built an integrated product platform with broad therapeutic potential in a variety of indications based on our lentiviral gene addition platform, gene editing and cancer immunotherapy capabilities. Our severe genetic disease ("SGD") programs include beti-cel, LentiGlobin for SCD gene therapy, and eli-cel. Our programs in oncology are focused on developing novel T cell-based immunotherapies, including CAR and TCR T cell therapies. bb2121 (idecabtagene vicleucel, or ide-cel), and bb21217 are CAR-T cell product candidates for the treatment of multiple myeloma and partnered under our collaboration arrangement with BMS.

We are commercializing beti-cel as ZYNTEGLO in the EU and began to treat patients in the commercial context in the first quarter of 2021. However, in February 2021 we temporarily suspended marketing of ZYNTEGLO in light of safety events in the HGB-206 clinical study of LentiGlobin for SCD, which is manufactured using the same vector as ZYNTEGLO. Additionally, the EMA has paused the renewal procedure for ZYNTEGLO's conditional marketing authorization while the EMA's pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary. We are engaged with the EMA in discussions regarding our proposed development plans for beti-cel as a treatment for patients with TDT who are less than 12 years of age and for patients who have a  $\beta^0/\beta^0$  genotype. We are engaged with the FDA in discussions regarding our proposed development plans for beti-cel as a treatment for patients with TDT. Contingent upon successful resolution of the FDA's concerns arising out of the safety events in our SCD program, we currently expect to complete our BLA submission for beti-cel in mid-2021 for the treatment of patients with TDT across all genotypes, including non- $\beta^0/\beta^0$  and  $\beta^0/\beta^0$  genotypes, and patients with TDT who are less than 12 years of age.

Based on our prior discussions with the FDA, we believe that we may be able to seek accelerated approval for LentiGlobin for SCD in the United States on the basis of clinical data from Group C of our HGB-206 clinical study, with our HGB-210 clinical study providing confirmatory data for full approval. However, in light of a SUSAR of acute myeloid leukemia and a SUSAR of myelodysplastic syndrome in our HGB-206 clinical study, the FDA has placed our clinical studies of LentiGlobin for SCD on clinical hold. We are investigating these events and plan to continue to work closely with the FDA in their review of these events. In addition, we are also engaged with the EMA in discussions regarding our proposed development plans for LentiGlobin for SCD in Europe.

In October 2020, the EMA accepted our Marketing Authorization Application in the EU for eli-cel for the treatment of patients with CALD. Based on our discussions with the FDA, we believe that we may be able to seek approval for eli-cel for the treatment of patients with CALD on the basis of our clinical data from our ongoing Starbeam study, safety data from our ongoing ALD-104 study, and the completed ALD-103 observational study. We currently expect to submit the BLA for eli-cel for the treatment of patients with CALD in mid-2021.

In collaboration with BMS, we are developing ide-cel and the bb21217 product candidates as treatments for multiple myeloma. We are co-developing and co-promoting ide-cel in the United States with BMS and we have exclusively licensed to BMS the development and commercialization rights for ide-cel outside of the United States. In September 2020, the FDA accepted for Priority Review the BLA submitted by BMS for ide-cel as a treatment for relapsed and refractory multiple myeloma. We have exclusively licensed the development and commercialization rights for the bb21217 product candidate to BMS, with an option for us to elect to co-develop and co-promote bb21217 within the United States. In addition, we are

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independently pursuing next-generation BCMA-targeting CAR-T approaches for treating multiple myeloma. Our other programs in oncology include preclinical programs to discover and develop T cell product candidates to treat other hematologic and solid tumor malignancies, including: non-Hodgkin's lymphoma, acute myeloid leukemia, MAGE-A4 positive solid tumors, and Merkel cell carcinoma.

Since our inception in 1992, we have devoted substantially all of our resources to our development efforts relating to our product candidates, including activities to manufacture product candidates in compliance with good manufacturing practices, or GMP, to conduct clinical studies of our product candidates, to provide selling, general and administrative support for these operations and to protect our intellectual property. We have not generated any revenue from product sales. We have funded our operations primarily through the sale of common stock in our public offerings, private placements of preferred stock and warrants and through collaborations.

As of December 31, 2020, we had cash, cash equivalents and marketable securities of approximately \$1.27 billion. We have never been profitable and have incurred net losses in each year since inception. Our net losses were \$618.7 million for the year ended December 31, 2020 and our accumulated deficit was \$2.90 billion as of December 31, 2020. Substantially all of our net losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. We expect to continue to incur significant expenses and operating losses for at least the next several years. We expect our expenses will increase substantially in connection with our ongoing and planned activities, as we:

- conduct clinical studies for our clinical programs in β-thalassemia, SCD, and ALD, fund our share of the costs of clinical studies for our program in multiple myeloma in collaboration with BMS, and advance our preclinical programs into clinical development;
- increase research and development-related activities for the discovery and development of product candidates in severe genetic diseases and oncology;
- manufacture clinical study materials and establish the infrastructure necessary to support and develop large-scale manufacturing capabilities to support commercialization of our product and any future products;
- seek regulatory approval for our product candidates;
- add personnel to support our product development and commercialization efforts;
- increase activities related to the commercialization of ZYNTEGLO in multiple markets in Europe, the potential commercial launch of beti-cel in the United States, and the potential commercial launches of additional late-stage product candidates in the United States and Europe; and
- incur costs related to the separation of our portfolio of programs and products in severe genetic disease and oncology into two separate, independent publicly traded companies.

As we seek to obtain regulatory approval for our product candidates and begin to commercialize ZYNTEGLO, we expect to incur significant commercialization expenses as we prepare for and begin product sales, marketing, commercial manufacturing, and distribution. Accordingly, until we generate significant revenues from product sales, we will seek to fund our operations through public or private equity or debt financings, strategic collaborations, or other sources. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our products.

Because of the numerous risks and uncertainties associated with product development and commercialization, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenues from the sale of our products, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

#### ***Business update***

Beginning in late 2019, the outbreak of a novel strain of coronavirus (COVID-19) has evolved into a global pandemic. As a result, we continue to experience disruptions and increased risk in our operations and those of third parties upon whom we rely, which may materially and adversely affect our business. These include disruptions and risks related to the conduct of our clinical trials, manufacturing, and commercialization efforts, as policies at various clinical sites and federal, state, local and foreign laws, rules and regulations continue to evolve, including quarantines, travel restrictions, and direction of healthcare resources toward pandemic response efforts. The COVID-19 pandemic has impacted the timing of patient treatment in the

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commercial context, and the timing of our ongoing clinical studies, with the result of slower patient enrollment and treatment in our clinical studies and delays in post-treatment follow up visits, the impact of which has varied by clinical study and by program. It has also affected our activities with and operations at our third-party manufacturers. It is unknown how long these disruptions could continue. In addition, we expect the COVID-19 pandemic to delay our ability to achieve market access and reimbursement for ZYNTEGLO in Europe due to shifting priorities of the local authorities and healthcare system. As a result of the demands upon healthcare regulatory authorities, review, inspection, and other activities related to review of regulatory submissions in drug development may be impacted, and may result in delays for an unknown period of time.

We continue to evaluate the impact of the COVID-19 global pandemic on patients, healthcare providers and our employees, as well as our operations and the operations of our business partners and healthcare communities. In response to the COVID-19 pandemic, we have implemented policies at our locations to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory or manufacturing facility, a work-from-home policy applicable to the majority of our personnel, and a phased approach to bringing personnel back to our locations over time. Given the importance of supporting our patients, we are diligently working with our suppliers, healthcare providers and partners to provide patients with access to ZYNTEGLO, while taking into account regulatory, institutional, and government guidance, policies and protocols. Further, we are working with our clinical study sites to understand the duration and scope of the impact on enrollment, develop protocols to help mitigate the impact of the COVID-19 pandemic, and other activities for our ongoing clinical studies. However, the ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments which are difficult to predict.

We expect our cash, cash equivalents and marketable securities of \$1.27 billion as of December 31, 2020, will be sufficient to fund planned operations for at least the next twelve months from the date of issuance of these financial statements, though we may pursue additional cash resources through public or private equity or debt financings or by establishing additional collaborations with other companies.

In January 2021, we announced our intent to separate our severe genetic disease and oncology programs into two separate, independent publicly traded companies, bluebird bio, Inc. and a new company, which we refer to as Oncology NewCo in this annual report on Form 10-K. bluebird bio, Inc. intends to retain focus on our severe genetic disease programs and Oncology NewCo is expected to focus on our oncology programs. The transaction is expected to be completed in late 2021 and is anticipated to be tax-free, subject to receipt of a favorable IRS ruling.

## **Financial operations overview**

### **Revenue**

To date, we have not generated any revenues from the sale of products. Our revenues have been derived from collaboration arrangements, out-licensing arrangements, research fees, and grant revenues.

To date, revenue recognized under our collaborative arrangements has been primarily generated from our collaboration arrangement with BMS. The terms of the arrangement with respect to ide-cel contain multiple promised goods or services, which include at inception: (i) research and development services, (ii) a license to ide-cel, and (iii) manufacture of vectors and associated payload for incorporation into ide-cel under the license. As of September 2017, the collaboration also included the following promised goods or services with respect to bb21217: (i) research and development services, (ii) a license to bb21217, and (iii) manufacture of vectors and associated payload for incorporation into bb21217 under the license. We entered into an agreement with BMS to co-develop and co-promote ide-cel in March 2018, which was subsequently amended in May 2020, in which both parties will share equally in U.S. costs and profits. Revenue from our collaborative arrangements is recognized as the underlying performance obligations are satisfied.

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* (“ASC 808”) to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606, *Revenue from Contracts with Customers* (“Topic 606” or “ASC 606”). For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. Amounts that are owed to collaboration partners are recognized as an offset to collaborative arrangement revenues as such amounts are incurred by the

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collaboration partner. Where amounts owed to a collaboration partner exceed our collaborative arrangement revenues in a quarterly period, such amounts in excess are classified as research and development expense. For those elements of the arrangement that are accounted for pursuant to Topic 606, we apply the five-step model prescribed in Topic 606.

Effective January 1, 2020, we adopted Accounting Standards Update ("ASU") No. 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606* ("ASU 2018-18") on a retrospective basis. As a result, prior periods are presented in accordance with the new standard. Prior to the adoption of ASU 2018-18, we presented all revenue recognized under our collaborative arrangements as collaboration revenue on our consolidated statement of operations and comprehensive loss. However, as we recognize revenue under our collaborative arrangements both within and outside the scope of Topic 606, we have revised our presentation of revenue on our consolidated statement of operations and comprehensive loss as follows: service revenue includes revenue from collaborative partners recognized within the scope of Topic 606 and collaborative arrangement revenue includes only revenue from collaborative partners recognized outside the scope of Topic 606.

Nonrefundable license fees are recognized as revenue upon delivery of the license provided there are no unsatisfied performance obligations in the arrangement. License revenue has historically been generated from out-license agreements, under which we may also recognize revenue from potential future milestone payments and royalties.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

#### ***Research and development expenses***

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with clinical research organizations ("CROs") and clinical sites that conduct our clinical studies;
- costs of acquiring, developing, and manufacturing inventory;
- reimbursable costs to our partners for collaborative activities;
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, information technology, insurance, and other supplies in support of research and development activities;
- costs associated with our research platform and preclinical activities;
- milestones and upfront license payments;
- costs associated with our regulatory, quality assurance and quality control operations; and
- amortization of certain intangible assets.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. We cannot determine with certainty the duration and completion costs of the current or future clinical studies of our product candidates or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may not succeed in achieving regulatory approval for all of our product candidates. The duration, costs, and timing of clinical studies and development of our product candidates will depend on a variety of factors, any of which could mean a significant change in the costs and timing associated with the development of our product candidates including:

- the scope, rate of progress, and expense of our ongoing as well as any additional clinical studies and other research and development activities we undertake;
- future clinical study results;
- uncertainties in clinical study enrollment rates;

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- new manufacturing processes or protocols that we may choose to or be required to implement in the manufacture of our lentiviral vector or drug product;
- regulatory feedback on requirements for regulatory approval, as well as changing standards for regulatory approval; and
- the timing and receipt of any regulatory approvals.

We plan to increase our research and development expenses for the foreseeable future as we continue to advance the development of beti-cel, eli-cel, and LentiGlobin for SCD, conduct research and development activities in severe genetic diseases and oncology, fund our share of the costs of development of ide-cel and bb21217 (if we exercise our option to co-develop and co-commercialize this product candidate) in collaboration with BMS, and continue the research and discovery of product candidates using our gene editing technology platform. Our research and development expenses include expenses associated with the following activities:

- Northstar-2 Study (HGB-207) - a multi-site, international phase 3 study to examine the safety and efficacy of beti-cel in the treatment of patients with TDT and a non- $\beta^0/\beta^0$  genotype.
- Northstar-3 Study (HGB-212) - a multi-site, international phase 3 study to examine the safety and efficacy of beti-cel in the treatment of patients with TDT and a  $\beta^0/\beta^0$  genotype or an IVS-I-110 mutation.
- HGB-206 study - a multi-site phase 1/2 study in the United States to study the safety and efficacy of LentiGlobin in the treatment of patients with SCD.
- HGB-210 study - our multi-site, international phase 3 study of LentiGlobin in patients with SCD and a history of vaso-occlusive events.
- Starbeam Study (ALD-102) - a multi-site, international phase 2/3 study to examine the safety and efficacy of eli-cel in the treatment of patients with CALD.
- ALD-104 study - our multi-site, international phase 3 study to examine the safety and efficacy of eli-cel after myeloablative conditioning using busulfan and fludarabine in the treatment of patients with CALD.
- CRB-401 study - an open label, single-arm, multi-center, phase 1 study to examine the safety and efficacy of ide-cel in the treatment of patients with relapsed and refractory multiple myeloma.
- KarMMA study - an open label, single-arm, multi-center phase 2 study to examine the efficacy and safety of ide-cel in the treatment of patients with relapsed and refractory multiple myeloma.
- KarMMA-2 study - a multi-cohort, open-label, multicenter phase 2 study to examine the safety and efficacy of ide-cel in the treatment of patients with relapsed and refractory multiple myeloma and in high-risk multiple myeloma.
- KarMMA-3 study - a multicenter, randomized, open-label phase 3 study comparing the efficacy and safety of ide-cel versus standard triplet regimens in patients with relapsed and refractory multiple myeloma.
- KarMMA-4 study - a multi-cohort, open-label, multicenter phase 1 study intended to determine the optimal target dose and safety of ide-cel in subjects with newly-diagnosed multiple myeloma.
- CRB-402 study - an open label, single-arm, multicenter, phase 1 study to examine the safety and efficacy of the bb21217 product candidate in the treatment of patients with relapsed and refractory multiple myeloma.
- We will continue to incur costs related to the manufacture of clinical study materials in support of our clinical studies.

We expect that the timing of investment in our ongoing clinical studies will reflect COVID-19 related delays in these studies.

Our direct research and development expenses consist principally of external costs, such as fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical studies, and costs related to acquiring and manufacturing clinical study materials. We allocate salary and benefit costs directly related to specific programs. We do not allocate personnel-related discretionary bonus or stock-based compensation costs, laboratory and related expenses, certain license and other collaboration costs, depreciation or other indirect costs that are deployed across multiple projects under development and, as such, the costs are separately classified as other research and development expenses in the table below:

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	Year ended December 31,		
	2020	2019	2018
beti-cel <sup>(1)</sup>	\$ 66,141	\$ 73,896	\$ 92,193
LentiGlobin for SCD	58,862	50,796	32,865
eli-cel	48,028	40,352	38,244
ide-cel	105,240	121,182	75,667
bb21217	23,511	19,827	15,624
Preclinical programs	45,888	49,700	50,115
Total direct research and development expense	347,670	355,753	304,708
Employee- and contractor-related expenses	63,840	52,617	35,697
Stock-based compensation expense	72,239	80,139	54,422
Laboratory and related expenses <sup>(2)</sup>	16,689	12,208	8,311
License and other collaboration expenses <sup>(2)</sup>	15,285	7,021	9,876
Facility expenses	67,464	67,274	32,158
Other expenses	4,769	7,401	3,417
Total other research and development expenses	240,286	226,660	143,881
Total research and development expense	\$ 587,956	\$ 582,413	\$ 448,589

(1)Following our receipt of conditional approval for the marketing authorization of ZYNTEGLO by the European Commission in June 2019, all manufacturing costs associated with the production of LentiGlobin for use in the commercial sale of ZYNTEGLO in the European Union will be evaluated for capitalization as inventory on our consolidated balance sheets.

(2)Prior to 2020, costs within these categories were disclosed as "platform-related expenses."

#### **Selling, general and administrative expenses**

Selling, general and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses for our employees in executive, operational, finance, legal, business development, commercial, information technology, and human resource functions. Other selling, general and administrative expenses include facility-related costs, professional fees for accounting, tax, legal and consulting services, directors' fees and expenses associated with obtaining and maintaining patents.

We anticipate that our selling, general and administrative expenses, including payroll and sales and marketing expenses, will continue to increase in the future relative to current levels as we execute on our commercial launch plans in Europe for ZYNTEGLO, and perform commercial readiness activities in the United States for our product candidates.

#### **Cost of royalty and other revenue**

Cost of royalty and other revenue represents expense associated with amounts owed to third-party licensors as a result of revenue recognized under our out-license arrangements.

#### **Change in fair value of contingent consideration**

On June 30, 2014, we acquired Precision Genome Engineering, Inc., or Pregenex. The agreement provided for up to \$135.0 million in future contingent cash payments by us upon the achievement of certain preclinical, clinical and commercial milestones related to the Pregenex technology.

As of December 31, 2020, there are \$120.0 million in future contingent cash payments, of which \$20.1 million relates to clinical milestones and \$99.9 million relates to commercial milestones. We estimate future contingent cash payments have a fair value of \$1.5 million as of December 31, 2020, which are classified within other non-current liabilities on our consolidated balance sheet.

[Table of Contents](#)***Interest income, net***

For the years ended December 31, 2020 and 2019, interest income, net consists primarily of interest income earned on investments. For the year ended December 31, 2018, interest income, net consisted primarily of interest income earned on investments and interest expense on the financing lease obligation for our headquarters at 60 Binney Street in Cambridge, Massachusetts. Upon adoption of ASU 2016-02, *Leases (Topic 842)* (“ASU 2016-02” or “ASC 842”) on January 1, 2019, we de-recognized the financing lease obligation and, as a result, no longer recognize interest expense associated with the financing lease obligation.

***Other (expense) income, net***

Other (expense) income, net consists primarily of gains and losses on equity securities held by us, gains and losses on disposal of fixed assets, and gains and losses on foreign currency transactions.

**Critical accounting policies and significant judgments and estimates**

Our management’s discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the U.S. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. In making estimates and judgments, management employs critical accounting policies.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this annual report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

***Revenue recognition******Revenue recognition***

Under Topic 606, *Revenue from Contracts with Customers*, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer’s discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations. The identification of material rights requires judgments related to the determination of the value of the underlying license relative to the option exercise price, including assumptions about technical feasibility and the probability of developing a candidate that would be subject to the option rights. The exercise of a material right is accounted for as a contract modification for accounting purposes.

We assess whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity’s promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, we consider factors such as the research, manufacturing and

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commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. We also consider the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices (“SSP”) on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, we consider applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. We validate the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, we estimate the amount of consideration to which we will be entitled in exchange for transferring the promised goods or services to a customer. We determine the amount of variable consideration by using the expected value method or the most likely amount method. We include the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee’s control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, we adjust consideration for the effects of the time value of money if the timing of payments provides us with a significant benefit of financing. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. We assessed each of our revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of our arrangements.

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

We recognize revenue within the following financial statement captions:

*Service revenue*

To date, our service revenue has primarily been generated from the elements of our collaboration arrangement with BMS that are accounted for pursuant to Topic 606, using the five-step model described above. As discussed further below, we analyze our collaboration arrangement to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* (“ASC 808”) or Topic 606. For the elements of the arrangement which are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606, we record the related revenue as service revenue on the consolidated statement of operations and comprehensive loss. Refer below for additional discussion around our policy for recognizing collaborative arrangement revenue and the determination of whether elements of a collaboration arrangement are within the scope of ASC 808 or Topic 606.

[Table of Contents](#)*Collaborative arrangement revenue*

To date, collaborative arrangement revenue has been primarily generated from our collaboration arrangements with BMS and Regeneron Pharmaceuticals, Inc. ("Regeneron"), as further described in Note 11, *Collaborative arrangements* in the notes to consolidated financial statements.

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808 to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606 (refer above for further discussion of the Company's policy for recognizing service revenue). For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. Amounts that are owed to collaboration partners are recognized as an offset to collaborative arrangement revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed our collaborative arrangement revenues in each quarterly period, such amounts are classified as research and development expense.

The recognition of service revenue and collaborative arrangement revenue (expense) require management judgment due to the fact that the terms of our collaboration arrangements are complicated and the nature of the collaborative activities change over time. This process includes the identification of costs that we incur that relate to each particular collaboration arrangement, evaluating the nature of these costs (for example, whether the costs relate to a particular geography or territory or whether the costs relate to clinical or commercial activities), and applying the terms of the respective collaborative arrangement to determine the portion of such costs that are the responsibility of the collaboration partner, which in certain circumstances requires significant judgment.

*Leases*

Effective January 1, 2019, we adopted ASU 2016-02, *Leases (Topic 842)*, ("ASU 2016-02" or "ASC 842"), using the required modified retrospective approach and utilizing the effective date as the date of initial application. As a result, prior periods are presented in accordance with the previous guidance in ASC 840, *Leases* ("ASC 840").

At the inception of an arrangement, we determine whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. We do not have material financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, we utilize our incremental borrowing rate to discount lease payments, which reflects the fixed rate at which we could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. To estimate our incremental borrowing rate, a credit rating applicable to us is estimated using a synthetic credit rating analysis since we do not currently have a rating agency-based credit rating. Prospectively, we will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

We have elected not to recognize leases with an original term of one year or less on the balance sheet. We typically only includes an initial lease term in our assessment of a lease arrangement. Options to renew a lease are not included in our assessment unless there is reasonable certainty that we will renew.

Assumptions that we made at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

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*ASC 842 transition practical expedients and application of transition provisions to leases at the transition date*

We elected the following practical expedients, which must be elected as a package and applied consistently to all of our leases at the transition date (including those for which we are a lessee or a lessor): i) we did not reassess whether any expired or existing contracts are or contain leases; ii) we did not reassess the lease classification for any expired or existing leases (that is, all existing leases that were classified as operating leases in accordance with ASC 840 are classified as operating leases, and all existing leases that were classified as capital leases in accordance with ASC 840 are classified as finance leases); and iii) we did not reassess initial direct costs for any existing leases.

For leases that existed prior to the date of initial application of ASC 842 (which were previously classified as operating leases), a lessee may elect to use either the total lease term measured at lease inception under ASC 840 or the remaining lease term as of the date of initial application of ASC 842 in determining the period for which to measure its incremental borrowing rate. In transition to ASC 842, we utilized the remaining lease term of its leases in determining the appropriate incremental borrowing rates.

*Application of ASC 842 policy elections to leases post adoption*

We have made certain policy elections to apply to our leases executed post adoption, or subsequent to January 1, 2019, as further described below.

In accordance with ASC 842, components of a lease should be split into three categories: lease components, non-lease components, and non-components. The fixed and in-substance fixed contract consideration (including any consideration related to non-components) must be allocated based on the respective relative fair values to the lease components and non-lease components.

Entities may elect not to separate lease and non-lease components. Rather, entities would account for each lease component and related non-lease component together as a single lease component. We have elected to account for lease and non-lease components together as a single lease component for all underlying assets and allocate all of the contract consideration to the lease component only.

ASC 842 allows for the use of judgment in determining whether the assumed lease term is for a major part of the remaining economic life of the underlying asset and whether the present value of lease payments represents substantially all of the fair value of the underlying asset. We apply the bright line thresholds referenced in ASC 842-10-55-2 to assist in evaluating leases for appropriate classification. The aforementioned bright lines are applied consistently to our entire portfolio of leases.

*Accrued research and development expenses*

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time.

We recognize expenses related to clinical studies based on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period and adjust accordingly.

Other examples of estimated accrued research and development expenses include fees paid to:

- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to the development, manufacturing, and distribution of clinical trial materials.

[Table of Contents](#)***Stock-based compensation***

We issue stock-based awards to employees and non-employees, generally in the form of stock options and restricted stock units. We account for our stock-based awards in accordance with FASB ASC Topic 718, *Compensation-Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. Prior to the adoption of Accounting Standards Update (“ASU”) No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After the adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award. Stock-based compensation costs for non-employees are recognized as expense over the vesting period on a straight-line basis.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees, non-employees, and directors, with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. We estimate the probability that certain performance criteria will be met and do not recognize compensation expense until it is probable that the performance-based vesting condition will be achieved.

We estimate the fair value of our stock-based awards to employees, non-employees, and directors, using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Effective January 1, 2020, we eliminated the use of a representative peer group and use only our own historical volatility data in our estimate of expected volatility given that there is now a sufficient amount of historical information regarding the volatility of our own stock price. We estimate the expected life of our employee stock options using the “simplified” method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

***Recent accounting pronouncements***

See Note 2, *Summary of significant accounting policies and basis of presentation*, in the notes to consolidated financial statements for a description of recent accounting pronouncements applicable to our business.

[Table of Contents](#)**Results of Operations***Comparison of the years ended December 31, 2020 and 2019:*

	Year ended December 31,		Change
	2020	2019	
	(in thousands)		
<b>Revenue:</b>			
Service revenue	\$ 114,064	\$ 30,729	\$ 83,335
Collaborative arrangement revenue	115,594	5,740	109,854
Royalty and other revenue	21,076	8,205	12,871
<b>Total revenues</b>	<b>250,734</b>	<b>44,674</b>	<b>206,060</b>
<b>Operating expenses:</b>			
Research and development	587,956	582,413	5,543
Selling, general and administrative	286,896	271,362	15,534
Cost of royalty and other revenue	5,396	2,978	2,418
Change in fair value of contingent consideration	(6,468)	2,747	(9,215)
<b>Total operating expenses</b>	<b>873,780</b>	<b>859,500</b>	<b>14,280</b>
Loss from operations	(623,046)	(814,826)	191,780
<b>Interest income, net</b>	<b>11,539</b>	<b>34,761</b>	<b>(23,222)</b>
<b>Other expense, net</b>	<b>(6,502)</b>	<b>(10,088)</b>	<b>3,586</b>
<b>Loss before income taxes</b>	<b>(618,009)</b>	<b>(790,153)</b>	<b>172,144</b>
<b>Income tax (expense) benefit</b>	<b>(686)</b>	<b>545</b>	<b>(1,231)</b>
<b>Net loss</b>	<b>\$ (618,695)</b>	<b>\$ (789,608)</b>	<b>\$ 170,913</b>

**Revenue.** Total revenue was \$250.7 million for the year ended December 31, 2020, compared to \$44.7 million for the year ended December 31, 2019. The increase of \$206.1 million was primarily attributable to a cumulative catch-up adjustment to revenue recorded in connection with the May 2020 BMS contract modification, as well as an increase in royalty and other revenue primarily attributable to revenue recognized under an out-license agreement with Juno Therapeutics, Inc.

**Research and development expenses.** Research and development expenses were \$588.0 million for the year ended December 31, 2020, compared to \$582.4 million for the year ended December 31, 2019. The increase of \$5.5 million was primarily attributable to the following:

- \$12.8 million of increased collaboration research funding costs, primarily due to an increase in collaboration costs incurred by BMS as a result of BMS assuming the contract manufacturing agreements relating to ide-cel adherent lentiviral vector under the May 2020 contract modification;
- \$8.2 million of increased net employee compensation, benefit, and other headcount related expenses, which is primarily driven by an increase in headcount in the quality and manufacturing organizations to support overall growth and includes a \$7.9 million decrease in stock-based compensation expense due to the recognition of expense on performance-based restricted stock units that vested in June 2019. Refer to Note 14, *Stock-based compensation*, in the notes to consolidated financial statements for discussion of stock-based compensation expense recognized on the performance-based restricted stock units;
- \$7.0 million of increased license and milestone fees primarily due to a sublicense fee upon execution of the May 2020 BMS contract modification; and
- \$5.3 million of increased consulting fees primarily related to the quality and manufacturing organizations.

These increased costs were partially offset by:

- \$17.6 million of decreased material production and other platform costs, primarily due to BMS assuming the contract manufacturing agreements relating to ide-cel adherent lentiviral vector under the May 2020 contract modification;
- \$7.0 million of decreased value-added taxes; and
- \$2.1 million of decreased medical research costs.

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**Selling, general and administrative expenses.** Selling, general and administrative expenses were \$286.9 million for the year ended December 31, 2020, compared to \$271.4 million for the year ended December 31, 2019. The increase of \$15.5 million was primarily due to the following:

- \$14.7 million of increased employee compensation, benefit, and other headcount related expenses, which is primarily driven by an increase in headcount in the information technology and human resource organizations to support overall growth, including an increase of \$3.9 million in stock-based compensation expense; and
- \$10.6 million of increased information technology and facility-related costs primarily due to increased investment in software applications and technology.

These increased costs were partially offset by:

- \$6.8 million of decreased costs related to commercial readiness activities due to delays in commercial launch activities during 2020 as a result of the COVID-19 pandemic; and
- \$2.3 million of decreased consulting fees primarily related to commercial strategy and product marketing.

**Cost of royalty and other revenue.** Cost of royalty and other revenue was \$5.4 million for the year ended December 31, 2020, compared to \$3.0 million for the year ended December 31, 2019. The increase is attributable to increased royalty revenue in the same periods.

**Change in fair value of contingent consideration.** The change in fair value of contingent consideration was primarily due to the change in significant unobservable inputs used in the fair value measurement of contingent consideration, including the probabilities of successful achievement of clinical and commercial milestones and discount rates.

**Interest income, net.** The decrease in interest income, net was primarily related to decreased interest income earned on investments due to an overall decrease in interest rates.

**Other expense, net.** The decrease in other expense, net was primarily related to changes in fair value on equity securities.

**Comparison of the years ended December 31, 2019 and 2018:**

	Year ended December 31,		Change
	2019	2018	
(in thousands)			
<b>Revenue:</b>			
Service revenue	\$ 30,729	\$ 44,533	\$ (13,804)
Collaborative arrangement revenue	5,740	7,820	(2,080)
Royalty and other revenue	8,205	2,226	5,979
<b>Total revenues</b>	<b>44,674</b>	<b>54,579</b>	<b>(9,905)</b>
<b>Operating expenses:</b>			
Research and development	582,413	448,589	133,824
Selling, general and administrative	271,362	174,129	97,233
Cost of royalty and other revenue	2,978	885	2,093
Change in fair value of contingent consideration	2,747	2,999	(252)
<b>Total operating expenses</b>	<b>859,500</b>	<b>626,602</b>	<b>232,898</b>
Loss from operations	(814,826)	(572,023)	(242,803)
<b>Interest income, net</b>	<b>34,761</b>	<b>14,624</b>	<b>20,137</b>
<b>Other (expense) income, net</b>	<b>(10,088)</b>	<b>1,961</b>	<b>(12,049)</b>
Loss before income taxes	(790,153)	(555,438)	(234,715)
Income tax benefit (expense)	545	(187)	732
<b>Net loss</b>	<b>\$ (789,608)</b>	<b>\$ (555,625)</b>	<b>\$ (233,983)</b>

**Revenue.** Total revenue was \$44.7 million for the year ended December 31, 2019, compared to \$54.6 million for the year ended December 31, 2018. The decrease of \$9.9 million was primarily attributable to a decrease in service revenue recognized for the ide-cel license and manufacturing services under our agreement with BMS. This decrease was partially offset by an

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increase in royalty and other revenue and an increase in collaborative arrangement revenue under our agreement with Regeneron.

**Research and development expenses.** Research and development expenses were \$582.4 million for the year ended December 31, 2019, compared to \$448.6 million for the year ended December 31, 2018. The increase of \$133.8 million was primarily attributable to the following:

- \$66.1 million of increased employee compensation, benefit, and other headcount related expenses, which is primarily driven by an increase in research and development headcount to support overall growth, including an increase of \$25.7 million in stock-based compensation expense. Refer to Note 14, *Stock-based compensation*, in the notes to consolidated financial statements for discussion of stock-based compensation expense recognized on the performance-based restricted stock units;
- \$34.8 million of increased IT and facility related costs, which includes the impact of adopting ASU 2016-02;
- \$26.3 million of increased collaboration research funding costs;
- \$13.1 million of increased laboratory expenses, material production, and other platform costs;
- \$9.7 million of increased research consulting and medical research costs; and
- \$3.6 million of increased clinical trial costs.

These increased costs were partially offset by \$20.6 million of decreased license and milestone fees.

**Selling, general and administrative expenses.** Selling, general and administrative expenses were \$271.4 million for the year ended December 31, 2019, compared to \$174.1 million for the year ended December 31, 2018. The increase of approximately \$97.2 million was primarily due to the following:

- \$65.3 million of increased employee compensation, benefit, and other headcount related expenses, which is primarily driven by an increase in selling, general, and administrative headcount to support overall growth, including an increase of \$24.1 million in stock-based compensation expense. Refer to Note 14, *Stock-based compensation*, in the notes to consolidated financial statements for discussion of stock-based compensation expense recognized on the performance-based restricted stock units;
- \$18.4 million of increased costs related to commercial-readiness activities; and
- \$13.2 million of increased consulting fees.

**Cost of royalty and other revenue.** Cost of royalty and other revenue was \$3.0 million for the year ended December 31, 2019, compared to \$0.9 million for the year ended December 31, 2018. The increase is attributable to increased royalty revenue in the same periods.

**Change in fair value of contingent consideration.** The change in fair value of contingent consideration was primarily due to the change in significant unobservable inputs used in the fair value measurement of contingent consideration, including the probabilities of successful achievement of clinical and commercial milestones and discount rates.

**Interest income, net.** The change in interest income, net was primarily related to increased interest income earned on investments, as well as a decrease in interest expense incurred due to the de-recognition of the financing lease obligation associated with our corporate headquarters at 60 Binney Street related to the adoption of ASU 2016-02 on January 1, 2019.

**Other (expense) income, net.** The change in other (expense) income, net was primarily related to changes in fair value on equity securities.

#### Liquidity and Capital Resources

As of December 31, 2020, we had cash, cash equivalents and marketable securities of approximately \$1.27 billion. We expect our cash, cash equivalents and marketable securities will be sufficient to fund planned operations for at least the next twelve months from the date of issuance of these financial statements, though we may pursue additional cash resources through public or private equity or debt financings or by establishing additional collaborations with other companies. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2020, our funds are primarily held in U.S. government agency securities and treasuries, equity securities, corporate bonds, commercial paper, and money market accounts.

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We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of December 31, 2020, we had an accumulated deficit of \$2.90 billion. We expect that our research and development and selling, general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through public or private equity or debt financings, strategic collaborations, or other sources. The likelihood of our long-term success must be considered in light of the expenses, difficulties, and potential delays to be encountered in the development and commercialization of new pharmaceutical products, competitive factors in the marketplace and the complex regulatory environment in which we operate. We may never achieve significant revenue or profitable operations.

We have funded our operations principally from the sale of common stock in public offerings and through our collaborations with BMS and Regeneron as outlined below:

- In January 2018, we sold 0.3 million shares of common stock pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the December 2017 underwritten public offering at a price of \$185.00 per share for aggregate net proceeds of \$48.7 million.
- In July 2018, we sold 3.9 million shares of common stock through an underwritten public offering at a price of \$162.50 per share for aggregate net proceeds to us of \$600.6 million.
- In August 2018, we sold 0.4 million shares of common stock to Regeneron in connection with our collaboration arrangement at a price of \$238.10 per share for aggregate net proceeds to us of \$100.0 million, of which \$45.5 million was attributed to a prepayment of joint research activities. See Note 11, *Collaborative arrangements*, in the notes to consolidated financial statements for more information.
- In May 2020, we entered into the First Amendment to the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement (as amended, the “Amended Ide-cel CCPS”) and the Second Amended and Restated bb21217 License Agreement (“Amended bb21217 License Agreement”) with BMS pursuant to which BMS modified its obligations to pay us for future ex-U.S. milestones and royalties on commercial sales by making a one-time up-front payment of \$200.0 million. See Note 11, *Collaborative arrangements*, in the notes to consolidated financial statements for more information.
- In May 2020, we sold 10.5 million shares of common stock (inclusive of shares sold pursuant to an option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$55.00 per share for aggregate net proceeds of \$541.5 million.

**Sources of Liquidity**

*Cash Flows*

The following table summarizes our cash flow activity:

	Year ended December 31,		
	2020	2019	2018
(in thousands)			
Net cash used in operating activities	\$ (470,351)	\$ (564,384)	\$ (413,426)
Net cash provided by (used in) investing activities	(84,345)	507,807	(679,435)
Net cash provided by financing activities	546,715	21,187	737,692
Decrease in cash, cash equivalents and restricted cash	\$ (7,981)	\$ (35,390)	\$ (355,169)

*Operating Activities.* The net cash used in operating activities was \$470.4 million for the year ended December 31, 2020 and primarily consisted of a net loss of \$618.7 million adjusted for non-cash items including stock-based compensation of \$156.6 million and depreciation and amortization of \$19.4 million, as well as the change in our net working capital.

The net cash used in operating activities was \$564.4 million for the year ended December 31, 2019 and primarily consisted of a net loss of \$789.6 million adjusted for non-cash items including stock-based compensation of \$160.6 million and depreciation and amortization of \$17.4 million, as well as the change in our net working capital.

The net cash used in operating activities was \$413.4 million for the year ended December 31, 2018 and primarily consisted of a net loss of \$555.6 million adjusted for non-cash items including stock-based compensation of \$110.8 million and depreciation and amortization of \$17.2 million, as well as the change in our net working capital.

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*Investing Activities.* Net cash used in investing activities for the year ended December 31, 2020 was \$84.3 million and was primarily due to the purchase of \$1.00 billion of marketable securities and the purchase of \$29.0 million of property, plant and equipment offset by proceeds from the maturities of available-for-sale marketable securities of \$918.3 million.

Net cash provided by investing activities for the year ended December 31, 2019 was \$507.8 million and was primarily due to proceeds from the maturities of available-for-sale marketable securities of \$1.34 billion offset by the purchase of \$756.6 million of marketable securities and the purchase of \$71.0 million of property, plant and equipment.

Net cash used in investing activities for the year ended December 31, 2018 was \$679.4 million and was primarily due to the purchase of \$1.52 billion of marketable securities and the purchase of \$55.7 million of property, plant and equipment offset by proceeds from the maturities of available-for-sale marketable securities of \$894.3 million.

*Financing Activities:* Net cash provided by financing activities for the year ended December 31, 2020 was \$546.7 million and was primarily due to net cash proceeds from our May 2020 common stock offering, as well as employee option exercises and ESPP contributions.

Net cash provided by financing activities for the year ended December 31, 2019 was \$21.2 million and was primarily due to net cash proceeds from employee option exercises and ESPP contributions.

Net cash provided by financing activities for the year ended December 31, 2018 was \$737.7 million and was primarily due to net cash proceeds from our January 2018 and July 2018 common stock offerings, as well as our issuance of common stock to Regeneron and employee option exercises and ESPP contributions.

### ***Contractual Obligations and Commitments***

#### ***Lease commitments***

##### ***60 Binney Street lease***

In September 2015, we entered into a lease agreement for office and laboratory space located at 60 Binney Street, Cambridge, Massachusetts. Under the terms of the lease, starting on October 1, 2016, we leased approximately 253,108 square feet of office and laboratory space at \$72.50 per square foot per year, or \$18.4 million per year in base rent, which is subject to scheduled annual rent increases of 1.75% plus certain operating expenses and taxes. The Company currently maintains a \$13.8 million collateralized letter of credit and, subject to the terms of the lease and certain reduction requirements specified therein, including market capitalization requirements, this amount may decrease to \$9.2 million over time. The lease will continue until March 31, 2027. Pursuant to a work letter entered into in connection with the lease, the landlord contributed an aggregate of \$42.4 million toward the cost of construction and tenant improvements for the building.

##### ***50 Binney Street sublease***

In April 2019, we entered into a sublease agreement for office space located at 50 Binney Street in Cambridge, Massachusetts (the “50 Binney Street Sublease”) to supplement our corporate headquarters located at 60 Binney Street in Cambridge, Massachusetts. Under the terms of the 50 Binney Street Sublease, we will lease 267,278 square feet of office space for \$99.95 per square foot, or \$26.7 million per year in base rent subject to certain operating expenses, taxes and annual rent increases of approximately 3%. The lease will commence when the space is available for use, which is anticipated to be in the first half of 2022, which reflects the sublessor’s exercise of its option to postpone the commencement date of the sublease, and end on December 31, 2030, unless other conditions specified in the 50 Binney Street Sublease occur. Upon signing the 50 Binney Street Sublease, we executed a \$40.1 million cash-collateralized letter of credit, which may be reduced in the future subject to the terms of the 50 Binney Street Sublease and certain reduction requirements specified therein. The \$40.1 million of cash collateralizing the letter of credit is classified as restricted cash and other non-current assets on our consolidated balance sheets. Payments will commence at the earlier of (i) the date which is 90 days following the commencement date and (ii) the date we take occupancy of all or any portion of the premises. In connection with the execution of the 50 Binney Street Sublease, we also entered into a Purchase Agreement for furniture and equipment (the “Furniture Purchase Agreement”) located on the premises upon lease commencement. Upon execution of the Furniture Purchase Agreement, we made an upfront payment of \$7.5 million, all of which was recorded within restricted cash and other non-current assets on our consolidated balance sheets as of December 31, 2020.

[Table of Contents](#)*Seattle, Washington leases*

In July 2018, we entered into a lease agreement for office and laboratory space located in a portion of a building in Seattle, Washington. The lease was amended in October 2018 to increase the total rentable space to approximately 36,126 square feet at \$54.00 per square foot in base rent per year, which is subject to scheduled annual rent increases of 2.5% plus certain operating expenses and taxes. The lease commenced on January 1, 2019 and the lease term will continue through January 31, 2027. The Company moved into the facility in June 2019. The lease allowed for a tenant improvement allowance of up to \$215.00 per square foot, or approximately \$8.0 million. We utilized the \$8.0 million tenant improvement allowance and it has been fully reimbursed by the landlord as of December 31, 2020.

In September 2019, we entered into a second amendment to the lease (the "Second Amendment"). The Second Amendment added approximately 22,188 square feet to the existing space and extended the lease term of the entire premises by 16 months, or until April 2028. Fixed monthly rent for the expanded space will be incurred at a rate of \$62.80 per square foot per year beginning in January 2021, subject to annual increases of 2.5%. The Second Amendment includes a five-year option to extend the term. In September 2020, the Company entered into a sublease agreement for the 22,188 square feet added under the Second Amendment at a fixed monthly rent of \$62.80 per square foot per year beginning in January 2021, subject to annual increases of 2.5%. The sublease term will continue through April 2028.

*Embedded leases*

In June 2016, we entered into a manufacturing agreement for the future commercial production of our beti-cel and eli-cel drug products with a contract manufacturing organization. Under this 12-year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, we paid \$12.0 million upon the achievement of certain contractual milestones. We paid \$5.0 million for the achievement of the first and second contractual milestones during 2016 and paid \$5.5 million for the third and fourth contractual milestones achieved during 2017. In March 2018, \$1.5 million of the possible \$2.0 million related to the fifth contractual milestone was achieved and was paid in the second quarter of 2018. Given that construction was completed in March 2018, beginning in April 2018 we will pay \$5.1 million per year in fixed suite fees as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services.

We may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. We concluded that this agreement contains an embedded lease as the suites are designated for our exclusive use during the term of the agreement. We concluded that we are not the deemed owner during construction nor is it a capital lease under ASC 840-10, Leases - Overall. As a result, in prior periods we accounted for the agreement as an operating lease under ASC 840 and recognized straight-line rent expense over the non-cancellable term of the embedded lease. As part of our adoption of ASC 842, effective January 1, 2019, we carried forward the existing lease classification under ASC 840. Additionally, we recorded a right-of-use asset and lease liability for this operating lease on the effective date and are recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In November 2016, we entered into an agreement for clinical and commercial production of our ZYNTEGLO, LentiGlobin for SCD, and eli-cel drug products with a contract manufacturing organization at an existing facility. We concluded that this agreement contains an embedded operating lease as the clean rooms are designated for our exclusive use during the term of the agreement. The term of the agreement is five years with subsequent three-year renewals at the mutual option of each party. As a result, we recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842, and are recognizing rent expense on a straight-line basis throughout the estimated remaining term of the embedded lease. In March 2020, we amended this agreement with the contract manufacturing organization, resulting in a lease modification. Under the terms of the amended arrangement, we may be required to pay annual maintenance and production fees of up to €16.5 million, depending on its production needs, and may terminate this agreement with twelve months' notice and a one-time termination fee. The amendment also provides for an option to reserve an additional clean room for a one-time option fee plus annual maintenance fees. As a result, we increased the right-of-use asset and lease liability related to this embedded operating lease during the first quarter of 2020.

In July 2020, we entered into an agreement reserving manufacturing capacity with a contract manufacturing organization. We concluded that this agreement contains an embedded lease as a controlled environment room at the facility is designated for our exclusive use during the term of the agreement, with the option to sublease the space if we provide notice that we will not utilize it for a specified duration of time. Under the terms of the agreement, we will be required to pay up to \$5.4 million per year in maintenance fees in addition to the cost of any services provided and may terminate this agreement with eighteen months' notice. The term of the agreement is five years, with the option to extend, and is expected to commence in the first half of 2021.

[Table of Contents](#)*Contingent Consideration Related to Business Combinations*

In connection with the Pregenac acquisition, we agreed to make contingent cash payments to the former equityholders of Pregenac. In accordance with accounting guidance for business combinations, these contingent cash payments are recorded as contingent consideration liabilities on our consolidated balance sheets at fair value. During the second quarter of 2017, a \$5.0 million preclinical milestone was achieved, which resulted in a \$5.0 million payment to the former equityholders of Pregenac during the third quarter of 2017. The aggregate remaining undiscounted amount of contingent consideration potentially payable is \$120.0 million. As of December 31, 2020, and 2019, \$1.5 million and \$8.0 million, respectively, is reflected as a non-current liability in the consolidated balance sheet, which represents the fair value of our contingent consideration obligations as of this date.

*Contingent Milestone and Royalty Payments*

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain development, regulatory and commercial milestones (such as the start of a clinical trial, filing of a BLA, approval by the FDA or product launch). We do not recognize these commitments in our financial statements until they become payable or have been paid.

Based on our development plans as of December 31, 2020, we may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with our collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. Because the achievement of these milestones or sales had not occurred as of December 31, 2020, such contingencies have not been recorded in our financial statements. Amounts related to contingent milestone payments and sales-based royalties are not yet considered contractual obligations as they are contingent upon success.

- Under a license agreement with Inserm-Transfert pursuant to which we license certain patents and know-how for use in adrenoleukodystrophy therapy, we will be required to make payments based upon development, regulatory and commercial milestones for any products covered by the in-licensed intellectual property. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €0.3, €0.2 and €1.6 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits. The royalty is subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.
- Under a license agreement with Institut Pasteur pursuant to which we license certain patents for use in *ex vivo* gene therapy, we will be required to make payments per product covered by the in-licensed intellectual property upon the achievement of development and regulatory milestones, depending on the indication and the method of treatment. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €1.5 and €2.0 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which varies slightly depending on the indication of the product. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the low single digits to mid-range double digits depending on the nature of the sublicense and stage of development. We are required to make an annual maintenance payment, which is creditable against royalty payments on a year-by-year basis. On April 1, 2015, we amended this license agreement with Institut Pasteur, which resulted in a payment of €3.0 million that was paid during the second quarter of 2015. During the year ended December 31, 2020 we paid Institut Pasteur €7.3 million in connection with amounts owed to us by sublicensees.
- Under a license agreement with the Board of Trustees of the Leland Stanford Junior University, or Stanford, pursuant to which we license the HEK293T cell line for use in gene therapy products, we are required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits that varies with net sales. The royalty is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.
- Under a license agreement with the Massachusetts Institute of Technology, or MIT, pursuant to which we license various patents, we will be required to make a payment of \$0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying

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from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.

- Under a license agreement with Research Development Foundation pursuant to which we license patents that involve lentiviral vectors, we will be required to make payments of \$1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten years following first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.
- Under a license agreement with Biogen Inc., pursuant to which we license certain patents and patent applications related to our ide-cel and bb21217 product candidates, we will be required to make certain payments related to certain development milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$23.0 million in the aggregate for each licensed product upon the achievement of remaining milestones. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay a percentage of net sales as a royalty in the low single digits.
- Under a license agreement with the National Institutes of Health, or NIH, pursuant to which we license certain patent applications related to our ide-cel and bb21217 product candidates, we have agreed to certain development and regulatory milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$9.7 million in the aggregate for a licensed product upon the achievement of these milestones. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay NIH a percentage of net sales as a royalty in the low single digits. The royalties payable under this license agreement are subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits. During the year ended December 31, 2020 we paid NIH \$1.0 million upon milestones reached for a product covered by in-licensed intellectual property.
- Under a license agreement with SIRION Biotech GmbH, or Sirion, pursuant to which we license certain patents directed to manufacturing related to our LentiGlobin product candidate, we will be required to make certain payments related to certain development milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to \$13.4 million in the aggregate for each product covered by the in-licensed intellectual property. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay Sirion a percentage of net sales as a royalty in the low single digits. The royalties payable under this license agreement are subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

*Other Funding Commitments*

We enter into contracts in the normal course of business with CROs for preclinical research studies and clinical trials, research supplies and other services and products for operating purposes. We have also entered into multi-year agreements with manufacturing partners in the United States and Europe (Brammer Bio, now part of Thermo Fisher Scientific, Inc., Novasep, now part of Thermo Fisher Scientific, Inc., and SAFC Carlsbad, Inc., or SAFC, a subsidiary of MilliporeSigma), which are partnering with us on production of lentiviral vector across all of our programs. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. and apceth Biopharma, or apceth, to produce drug product for Lenti-D, LentiGlobin and bb21217. Currently, SAFC is the sole manufacturer of the lentiviral vector and apceth is the sole manufacturer of the drug product to support commercialization of ZYNTEGLO in Europe for the treatment of TDT. In our manufacturing agreement with SAFC, we are required to provide rolling forecasts for products on a quarterly basis, a portion of which will be considered a binding, firm order, subject to a purchase commitment. In our manufacturing agreement with apceth, we reserve production capacity for the manufacture of our drug product. BMS manufactures drug product for ide-cel. Our total non-cancelable contractual obligations arising from these manufacturing agreements is \$96.5 million, with \$83.9 million of these obligations due within the next twelve months. We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions and potential commercial launch. We are engaging with apheresis and infusion centers, which we refer to as qualified treatment centers, that will be the centers for collection of HSCs from the patient and for infusion of drug product to the patient. For the treatment of patients with our drug product in the commercial setting, we are entering into agreements with participating qualified treatment centers in the jurisdictions where we plan to commercialize our products. These contracts generally provide for termination on notice. Wherever contracts include stipulated commitment payments, we have included such payments in the table of contractual obligations and commitments.

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**Off-Balance Sheet Arrangements**

As of December 31, 2020, we did not have any off-balance sheet arrangements as defined in the rules and regulations of the SEC.

[Table of Contents](#)**Item 7A. Quantitative and Qualitative Disclosures About Market Risks**

We are exposed to market risk related to changes in interest rates. As of December 31, 2020 and 2019, we had cash, cash equivalents and marketable securities of \$1.27 billion and \$1.24 billion, respectively, primarily invested in U.S. Treasury securities, U.S. government agency securities, equity securities, corporate bonds, commercial paper and money market accounts. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points, or one percentage point, from levels at December 31, 2020, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of \$4.4 million.

**Item 8. Financial Statements and Supplementary Data**

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

**Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure**

None.

**Item 9A. Controls and Procedures*****Evaluation of Disclosure Controls and Procedures***

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13(a)- 15(e) and 15(d)- 15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")), as of the end of the period covered by this Annual Report on Form 10-K. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective.

***Management's Annual Report on Internal Control Over Financial Reporting***

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13(a)-15(f) and 15(d)-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Under the supervision and with the participation of management, including our principal executive and financial officers, we assessed our internal control over financial reporting as of December 31, 2020, based on criteria for effective internal control over financial reporting established in Internal Control - Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2020, based on criteria established in the COSO 2013 framework.

The effectiveness of our internal control over financial reporting as of December 31, 2020 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

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***Inherent Limitations of Internal Controls***

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within our company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

***Changes in Internal Control over Financial Reporting***

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13(a)-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, during the fourth quarter of 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

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**Report of Independent Registered Public Accounting Firm**

To the Stockholders and the Board of Directors of bluebird bio, Inc.

**Opinion on Internal Control over Financial Reporting**

We have audited bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, bluebird bio, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes and our report dated February 23, 2021 expressed an unqualified opinion thereon.

**Basis for Opinion**

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

**Definition and Limitations of Internal Control Over Financial Reporting**

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 23, 2021

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**Item 9B. Other Information**

Our policy governing transactions in our securities by our directors, officers, and employees permits our officers, directors and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended. We have been advised that certain of our officers (including Jason Cole (Chief Operating and Legal Officer) and David Davidson (Chief Medical Officer)) have entered into trading plans covering periods after the date of this annual report on Form 10-K in accordance with Rule 10b5-1 and our policy governing transactions in our securities. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company. We do not undertake to report Rule 10b5-1 trading plans that may be adopted by any officers or directors in the future, or to report any modifications or termination of any publicly announced trading plan, except to the extent required by law.

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**PART III**

**Item 10. Directors, Executive Officers and Corporate Governance**

Incorporated by reference from the information in our Proxy Statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 11. Executive Compensation**

Incorporated by reference from the information in our Proxy Statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters**

Incorporated by reference from the information in our Proxy Statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 13. Certain Relationships and Related Transactions and Director Independence**

Incorporated by reference from the information in our Proxy Statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

**Item 14. Principal Accountant Fees and Services**

Incorporated by reference from the information in our Proxy Statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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**PART IV**

**Item 15. Exhibits and Financial Statement Schedules**

(a)(1) Financial Statements.

The response to this portion of Item 15 is set forth under Item 8 above.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Consolidated Financial Statements or Notes thereto set forth under Item 8 above.

(a)(3) Exhibits.

See the Exhibit Index immediately before the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are filed or incorporated by reference as part of this Annual Report on Form 10-K.

**Item 16. Form 10-K Summary**

Not applicable.

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**bluebird bio, Inc.**

**Index to Consolidated Financial Statements**

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**Report of Independent Registered Public Accounting Firm**

To the Stockholders and the Board of Directors of bluebird bio, Inc.

**Opinion on the Financial Statements**

We have audited the accompanying consolidated balance sheets of bluebird bio, Inc. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 23, 2021 expressed an unqualified opinion thereon.

**Adoption of ASU No. 2016-02**

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases* (Topic 842), and the related amendments.

**Basis for Opinion**

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

**Critical Audit Matters**

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

[Table of Contents](#)***Amendment to the Bristol-Myers Squibb Collaboration Agreement******Description of the Matter***

As discussed in Note 11 to the consolidated financial statements, the Company and Bristol-Myers Squibb (BMS) entered into the First Amendment to the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement for Idecabtagene vicleucel (ide-cel) and the Second Amended and Restated License Agreement for bb21217 (collectively with the First Amendment to the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement for Idecabtagene vicleucel, the “Amendments”). The Amendments reduced the scope of the Company's ongoing performance obligations for vector manufacturing services through development for both ide-cel and bb21217 and resolved the uncertainty associated with certain previously constrained variable consideration included in the prior agreements. The Company allocated the \$200.0 million up-front payment received in connection with the Amendments to the remaining performance obligations pursuant to the variable consideration allocation exception.

Auditing management's application of the contract modification guidance under ASC 606, *Revenue from contracts with customers* to the Amendments was especially challenging due to the complicated contractual terms of the prior agreements and the Amendments and the information necessary to determine the nature and extent of changes to previously identified performance obligations was obtained from multiple sources. In addition, auditing management's evaluation that the up-front payment received in connection with the Amendments (i) related specifically to the Company's satisfaction of each of its remaining performance obligations and (ii) was representative of the amount of consideration the Company expected to be entitled to in exchange for satisfying the respective performance obligations, and thus was subject to the variable consideration allocation exception, required significant judgment.

***How We Addressed the Matter in Our Audit***

We obtained an understanding, evaluated the design and tested the operating effectiveness of internal controls that addressed the information used in and the identified risks related to the Company's process for accounting for amendments to its collaboration agreements.

To test the Company's application of the contract modification guidance under ASC 606 to the Amendments and assess the application of the variable consideration allocation exception, our procedures included, among others, inspecting the Amendments, obtaining information from the Company's personnel that oversee the collaboration activities and participated in the negotiations of the Amendments, understanding the nature of and basis for determining the up-front consideration received in connection with the Amendments and inspecting the associated model used to determine the amount of consideration to be received, and evaluating the application of the variable consideration allocation exception based on the nature of the previously constrained variable consideration and the performance obligations remaining to be satisfied.

[Table of Contents](#)***Bristol-Myers Squibb Ide-cel Co-Development, Co-Promote and Profit Share Agreement*****Description of the Matter**

As discussed in Notes 2 and 11 to the consolidated financial statements, the Company recognizes amounts received pursuant to collaboration arrangements in which both parties are active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of those activities as collaborative arrangement revenue, with an offset for amounts owed to the collaboration partner. Where amounts owed to a collaboration partner exceed the Company's collaborative arrangement revenue from the collaboration partner in a quarterly period, such amounts are classified as research and development expense. The process of recognizing collaborative arrangement revenue (expense) for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement includes the identification of costs incurred by the Company that relate to the collaboration arrangement, evaluating the nature of such costs, and applying the terms of the collaborative arrangement to determine the portion of such costs that are the responsibility of BMS. The process also includes an assessment of the costs incurred and reported by BMS, as well as the determination of the appropriate financial statement presentation in each quarterly reporting period. The Company recorded collaborative arrangement revenue for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement of \$108.2 million, net of collaborative partner amounts, and collaborative arrangement expense (included as a component of research and development expense) of \$41.6 million, net of collaborative arrangement revenue, for the year ended December 31, 2020.

Auditing collaborative arrangement revenue (expense) for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement is especially complex due to the fact that the contractual terms of the arrangement are complicated, the information necessary to determine collaborative arrangement revenue (expense) is accumulated from multiple sources and, in certain circumstances, the determination of (i) whether amounts incurred are eligible to be included in the determination of collaborative arrangement revenue (expense) or (ii) the portion of costs incurred that are the responsibility of BMS requires judgment.

**How We Addressed the Matter in Our Audit**

We obtained an understanding, evaluated the design and tested the operating effectiveness of internal controls that addressed the information used in and the identified risks related to the Company's process for recording collaborative arrangement revenue (expense) for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement.

To test the Company's collaborative arrangement revenue (expense) for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement, our procedures included, among others, inspecting the Company's collaboration agreement, comparing the Company's computations of collaborative arrangement revenue (expense) to the contractual terms of its collaboration arrangement, testing the accuracy and completeness of the underlying data used in the computation of collaborative arrangement revenue (expense), and evaluating the costs included in the computation of collaborative arrangement revenue (expense) based on the nature of the costs and the relevant contractual terms. We also obtained information directly from the Company's collaboration partner regarding the costs incurred by the collaboration partner during the period and agreed those amounts to the Company's computation of collaborative arrangement revenue (expense) for the BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement.

***Accrued Clinical and Contract Research Organization Costs and Manufacturing Costs*****Description of the Matter**

As discussed in Notes 2 and 7 to the consolidated financial statements, the Company records costs for clinical trial activities and manufacturing activities based upon estimates of costs incurred through the balance sheet date that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants, contract manufacturing organizations or other vendors. The Company's accruals for clinical and contract research organization costs and manufacturing costs totaled \$46.3 million at December 31, 2020.

Auditing the Company's accruals for clinical and contract research organization costs and manufacturing costs is especially complex due to the fact that information necessary to estimate the accruals is accumulated from multiple sources. In addition, in certain circumstances, the determination of the nature and level of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the level of services provided and there may be delays in invoicing from clinical study sites and other vendors.

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*How We Addressed  
the Matter in Our  
Audit*

We obtained an understanding, evaluated the design and tested the operating effectiveness of internal controls that addressed the information used in and the identified risks related to the Company's process for recording accrued clinical and contract research organization costs and manufacturing costs.

To test the completeness and valuation of the accruals for clinical and contract research organization costs and manufacturing costs, we performed audit procedures that included, among others, reading certain contracts with contract research organizations, contract manufacturing organizations, and clinical study sites to evaluate financial and certain other contractual terms, and testing the accuracy and completeness of the underlying data used in the accrual computations. We also compared the progress of clinical trials and the progress of manufacturing completed through the balance sheet date with information provided by the Company's operations personnel that oversee the clinical trials and manufacturing activities. Additionally, we obtained information directly from certain clinical study sites and contract manufacturing organizations which indicated the progress of clinical trials and the progress of manufacturing completed through the balance sheet date and compared that to the Company's accrual computations.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2012.  
Boston, Massachusetts  
February 23, 2021

[Table of Contents](#)**bluebird bio, Inc.****Consolidated Balance Sheets  
(in thousands, except per share amounts)**

	<b>As of December 31,</b>	
	<b>2020</b>	<b>2019</b>
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 317,705	\$ 327,214
Marketable securities	833,546	779,246
Prepaid expenses	37,472	32,888
Receivables and other current assets	26,814	12,826
Total current assets	1,215,537	1,152,174
Marketable securities	122,891	131,506
Property, plant and equipment, net	162,831	151,176
Intangible assets, net	10,041	14,326
Goodwill	13,128	13,128
Operating lease right-of-use assets	184,019	185,885
Restricted cash and other non-current assets	72,805	79,229
Total assets	\$ 1,781,252	\$ 1,727,424
<b>Liabilities and Stockholders' Equity</b>		
Current liabilities:		
Accounts payable	\$ 21,602	\$ 42,995
Accrued expenses and other current liabilities	145,406	141,556
Operating lease liability, current portion	25,024	20,175
Deferred revenue, current portion	2,320	8,474
Collaboration research advancement, current portion	9,236	10,380
Total current liabilities	203,588	223,580
Deferred revenue, net of current portion	25,762	9,791
Collaboration research advancement, net of current portion	21,581	27,834
Operating lease liability, net of current portion	167,997	170,812
Other non-current liabilities	7,268	10,414
Total liabilities	\$ 426,196	\$ 442,431
Commitments and contingencies <i>Note 9</i>		
Stockholders' equity:		
Preferred stock, \$0.01 par value, 5,000 shares authorized; 0 shares issued and outstanding at December 31, 2020 and December 31, 2019	\$ -	\$ -
Common stock, \$0.01 par value, 125,000 shares authorized; 66,432 and 55,368 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	665	554
Additional paid-in capital	4,260,443	3,568,184
Accumulated other comprehensive loss	(5,505)	(1,893)
Accumulated deficit	(2,900,547)	(2,281,852)
Total stockholders' equity	1,355,056	1,284,993
Total liabilities and stockholders' equity	\$ 1,781,252	\$ 1,727,424

*See accompanying notes to consolidated financial statements.*

[Table of Contents](#)**bluebird bio, Inc.****Consolidated Statements of Operations and Comprehensive Loss**  
(in thousands, except per share amounts)

	Year ended December 31,		
	2020	2019	2018
<b>Revenue:</b>			
Service revenue	\$ 114,064	\$ 30,729	\$ 44,533
Collaborative arrangement revenue	115,594	5,740	7,820
Royalty and other revenue	21,076	8,205	2,226
<b>Total revenues</b>	<b>250,734</b>	<b>44,674</b>	<b>54,579</b>
<b>Operating expenses:</b>			
Research and development	587,956	582,413	448,589
Selling, general and administrative	286,896	271,362	174,129
Cost of royalty and other revenue	5,396	2,978	885
Change in fair value of contingent consideration	(6,468)	2,747	2,999
<b>Total operating expenses</b>	<b>873,780</b>	<b>859,500</b>	<b>626,602</b>
Loss from operations	(623,046)	(814,826)	(572,023)
Interest income, net	11,539	34,761	14,624
Other (expense) income, net	(6,502)	(10,088)	1,961
<b>Loss before income taxes</b>	<b>(618,009)</b>	<b>(790,153)</b>	<b>(555,438)</b>
Income tax (expense) benefit	(686)	545	(187)
<b>Net loss</b>	<b>\$ (618,695)</b>	<b>\$ (789,608)</b>	<b>\$ (555,625)</b>
Net loss per share - basic and diluted	\$ (9.95)	\$ (14.31)	\$ (10.68)
Weighted-average number of common shares used in computing net loss per share - basic and diluted	62,178	55,191	52,032
<b>Other comprehensive (loss) income:</b>			
Other comprehensive (loss) income, net of tax benefit (expense) of \$0.0 million, \$(1.2) million and \$(0.4) million for the years ended December 31, 2020, 2019 and 2018, respectively	(3,612)	1,734	578
Total other comprehensive (loss) income	(3,612)	1,734	578
<b>Comprehensive loss</b>	<b>\$ (622,307)</b>	<b>\$ (787,874)</b>	<b>\$ (555,047)</b>

*See accompanying notes to consolidated financial statements.*

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**bluebird bio, Inc.**  
**Consolidated Statements of Stockholders' Equity**  
(in thousands)

	Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Accumulated deficit	Total stockholders' equity
	Shares	Amount				
<b>Balances at December 31, 2017</b>	49,406	\$ 494	\$ 2,540,951	\$ (4,205)	\$ (913,808)	\$ 1,623,432
Adjustment to beginning accumulated deficit from adoption of ASU 2014-09	-	-	-	-	(29,375)	(29,375)
Vesting of restricted stock units	152	2	(2)	-	-	-
Issuance of common stock upon public offering, net of issuance costs of \$34,588	4,169	42	649,326	-	-	649,368
Issuance of common stock to Regeneron	420	4	54,480	-	-	54,484
Exercise of stock options	575	5	29,763	-	-	29,768
Purchase of common stock under ESPP	16	-	1,604	-	-	1,604
Stock-based compensation	-	-	110,836	-	-	110,836
Other comprehensive income	-	-	-	578	-	578
Net loss	-	-	-	-	(555,625)	(555,625)
<b>Balances at December 31, 2018</b>	<b>54,738</b>	<b>\$ 547</b>	<b>\$ 3,386,958</b>	<b>\$ (3,627)</b>	<b>\$ (1,498,808)</b>	<b>\$ 1,885,070</b>
Adjustment to beginning accumulated deficit from adoption of ASU 2016-02	-	-	-	-	6,564	6,564
Vesting of restricted stock units	251	3	(3)	-	-	-
Exercise of stock options	354	4	17,834	-	-	17,838
Purchase of common stock under ESPP	25	-	2,766	-	-	2,766
Stock-based compensation	-	-	160,629	-	-	160,629
Other comprehensive income	-	-	-	1,734	-	1,734
Net loss	-	-	-	-	(789,608)	(789,608)
<b>Balances at December 31, 2019</b>	<b>55,368</b>	<b>\$ 554</b>	<b>\$ 3,568,184</b>	<b>\$ (1,893)</b>	<b>\$ (2,281,852)</b>	<b>\$ 1,284,993</b>
Issuance of common stock upon public offering, net of issuance costs of \$33,645	10,455	105	541,431	-	-	541,536
Vesting of restricted stock units	434	4	(4)	-	-	-
Exercise of stock options	95	1	1,846	-	-	1,847
Purchase of common stock under ESPP	80	1	3,774	-	-	3,775
Stock-based compensation	-	-	145,212	-	-	145,212
Other comprehensive loss	-	-	-	(3,612)	-	(3,612)
Net loss	-	-	-	-	(618,695)	(618,695)
<b>Balances at December 31, 2020</b>	<b>66,432</b>	<b>\$ 665</b>	<b>\$ 4,260,443</b>	<b>\$ (5,505)</b>	<b>\$ (2,900,547)</b>	<b>\$ 1,355,056</b>

*See accompanying notes to consolidated financial statements.*

[Table of Contents](#)**bluebird bio, Inc.****Consolidated Statements of Cash Flows  
(in thousands)**

	<b>Year ended December 31,</b>		
	<b>2020</b>	<b>2019</b>	<b>2018</b>
<b>Cash flows from operating activities:</b>			
Net loss	\$ (618,695)	\$ (789,608)	\$ (555,625)
Adjustments to reconcile net loss to net cash used in operating activities:			
Change in fair value of contingent consideration	(6,468)	2,747	2,999
Depreciation and amortization	19,356	17,434	17,158
Stock-based compensation expense	156,631	160,629	110,836
Unrealized loss (gain) on equity securities	7,217	9,297	(2,154)
Other non-cash items	458	(11,000)	(5,880)
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(10,089)	(13,913)	(24,288)
Operating lease right-of-use assets	21,281	22,496	-
Accounts payable	(20,100)	23,600	3,614
Accrued expenses and other liabilities	(4,982)	46,291	37,832
Operating lease liabilities	(17,380)	(9,944)	-
Deferred revenue	9,817	(16,674)	(41,872)
Collaboration research advancement	(7,397)	(5,739)	43,954
Net cash used in operating activities	<u>(470,351)</u>	<u>(564,384)</u>	<u>(413,426)</u>
<b>Cash flows from investing activities:</b>			
Purchase of property, plant and equipment	(28,986)	(71,028)	(55,737)
Purchases of marketable securities	(1,003,525)	(756,570)	(1,517,982)
Sales of marketable securities	29,878	-	-
Proceeds from maturities of marketable securities	918,288	1,340,629	894,284
Purchase of intangible assets	-	(5,224)	-
Net cash provided by (used in) investing activities	<u>(84,345)</u>	<u>507,807</u>	<u>(679,435)</u>
<b>Cash flows from financing activities:</b>			
Reimbursement of assets under financing lease obligation	-	-	3,098
Payments on financing lease obligation	-	-	(1,017)
Proceeds from public offering of common stock, net of issuance costs	541,536	-	649,368
Proceeds from exercise of stock options and ESPP contributions	5,179	21,187	31,759
Proceeds from issuance of common stock to Regeneron	-	-	54,484
Net cash provided by financing activities	<u>546,715</u>	<u>21,187</u>	<u>737,692</u>
Decrease in cash, cash equivalents and restricted cash	(7,981)	(35,390)	(355,169)
Cash, cash equivalents and restricted cash at beginning of year	381,709	417,099	772,268
Cash, cash equivalents and restricted cash at end of year	<u>\$ 373,728</u>	<u>\$ 381,709</u>	<u>\$ 417,099</u>
<b>Reconciliation of cash, cash equivalents and restricted cash:</b>			
Cash and cash equivalents	\$ 317,705	\$ 327,214	\$ 402,579
Restricted cash included in receivables and other current assets	\$ 1,500	\$ -	\$ 364
Restricted cash included in restricted cash and other non-current assets	\$ 54,523	\$ 54,495	\$ 14,156
Total cash, cash equivalents and restricted cash	<u>\$ 373,728</u>	<u>\$ 381,709</u>	<u>\$ 417,099</u>
<b>Supplemental cash flow disclosures:</b>			
Purchases of property, plant and equipment included in accounts payable and accrued expenses	\$ 2,854	\$ 5,286	\$ 7,449
Right-of-use assets obtained in exchange for operating lease liabilities	\$ 19,414	\$ 23,939	\$ -
Cash paid during the period for interest	\$ -	\$ -	\$ 15,494
Cash paid during the period for income taxes	\$ 361	\$ 637	\$ 358

*See accompanying notes to consolidated financial statements.*

[Table of Contents](#)**bluebird bio, Inc.**

**Notes to Consolidated Financial Statements  
For the Years Ended December 31, 2020, 2019 and 2018**

**1. Description of the business**

bluebird bio, Inc. (the “Company” or “bluebird”) was incorporated in Delaware on April 16, 1992, and is headquartered in Cambridge, Massachusetts. The Company is a biotechnology company committed to researching, developing and commercializing potentially transformative gene therapies for severe genetic diseases and cancer. Since its inception, the Company has devoted substantially all of its resources to its research and development efforts relating to its product candidates, including activities to manufacture product candidates, conduct clinical studies of its product candidates, perform preclinical research to identify new product candidates and provide selling, general and administrative support for these operations, including commercial-readiness activities.

The Company’s programs in severe genetic diseases include betibeglogene autotemcel (beti-cel; formerly LentiGlobin for β-thalassemia gene therapy) as a treatment for transfusion-dependent β-thalassemia, or TDT; its LentiGlobin® product candidate as a treatment for sickle cell disease, or SCD; and elivaldogene autotemcel (eli-cel; formerly Lenti-D gene therapy) as a treatment for cerebral adrenoleukodystrophy, or CALD. The Company’s programs in oncology are focused on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies. Idecabtagene vicleucel, or ide-cel, and bb21217 are product candidates in oncology under the Company’s collaboration arrangement with Bristol-Myers Squibb (“BMS”). ide-cel and bb21217 are CAR T cell product candidates for the treatment of multiple myeloma. Please refer to Note 11, *Collaborative arrangements*, for further discussion of the Company’s collaboration with BMS.

In June 2019, the Company received conditional marketing authorization from the European Commission for beti-cel as a treatment of patients 12 years and older with TDT who do not have a  $\beta^0/\beta^0$  genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte-matched related HSC donor is not available. beti-cel is being marketed as ZYNTEGLO™ in the European Union. Since receiving conditional marketing authorization for ZYNTEGLO, the Company has continued to advance its commercial readiness activities. Through December 31, 2020, the Company had not generated any revenue from product sales. In February 2021 the Company temporarily suspended marketing of ZYNTEGLO in light of safety events in the HGB-206 study of LentiGlobin gene therapy for SCD which is manufactured using the same vector as ZYNTEGLO. Additionally, the European Medicines Agency, or EMA, has paused the renewal procedure for ZYNTEGLO’s conditional marketing authorization while the EMA’s pharmacovigilance risk assessment committee reviews the risk-benefit assessment for ZYNTEGLO and determines whether any additional pharmacovigilance measures are necessary.

In January 2021, the Company announced its intent to separate its severe genetic disease and oncology programs into two separate, independent publicly traded companies, bluebird bio, Inc. and a new company, referred to as Oncology NewCo in these consolidated financial statements. bluebird bio, Inc. intends to retain focus on its severe genetic disease programs and Oncology NewCo is expected to focus on the Company’s oncology programs. The transaction is expected to be completed in late 2021 and is anticipated to be tax-free, subject to receipt of a favorable Internal Revenue Service (“IRS” ruling).

In accordance with Accounting Standards Codification (“ASC”) 205-40, *Going Concern*, the Company evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about its ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. The Company has incurred losses since inception and to date has financed its operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. As of December 31, 2020, the Company had an accumulated deficit of \$2.90 billion. During the year ended December 31, 2020, the Company incurred a loss of \$618.7 million and used \$470.4 million of cash in operations. The Company expects to continue to generate operating losses and negative operating cash flows for the next few years and will need additional funding to support its planned operating activities through profitability. The transition to profitability is dependent upon the successful development, approval, and commercialization of the Company’s products and product candidates and the achievement of a level of revenues adequate to support its cost structure.

As of December 31, 2020, the Company had cash, cash equivalents and marketable securities of \$1.27 billion. The Company expects its cash, cash equivalents and marketable securities will be sufficient to fund current planned operations for at least the next twelve months from the date of issuance of these financial statements, though it may pursue additional cash resources through public or private equity or debt financings or by establishing additional collaborations with other companies. Management’s expectations with respect to its ability to fund current planned operations is based on estimates that are subject to

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risks and uncertainties. If actual results are different from management's estimates, the Company may need to seek additional strategic or financing opportunities sooner than would otherwise be expected. However, there is no guarantee that any of these strategic or financing opportunities will be executed or executed on favorable terms, and some could be dilutive to existing stockholders. If the Company is unable to obtain additional funding on a timely basis, it may be forced to significantly curtail, delay, or discontinue one or more of its planned research or development programs or be unable to expand its operations or otherwise capitalize on its commercialization of its product and product candidates.

## **2. Summary of significant accounting policies and basis of presentation**

### ***Basis of presentation***

The accompanying consolidated financial statements have been prepared by the Company in accordance with accounting principles generally accepted in the United States ("GAAP") as found in the ASC and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States GAAP as found in the ASC and ASUs of the FASB.

Certain items in the prior year's consolidated financial statements have been reclassified to conform to the current presentation. No subtotals in the prior year consolidated financial statements were impacted by these reclassifications.

Amounts reported are computed based on thousands, except percentages, per share amounts or as otherwise noted. As a result, certain totals may not sum due to rounding.

### ***Principles of consolidation***

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

The Company continually assesses whether it is the primary beneficiary of a variable interest entity as changes to existing relationships or future transactions may result in consolidation or deconsolidation of one or more collaborators or partners. In determining whether it is the primary beneficiary of an entity in which the Company has a variable interest, management applies a qualitative approach that determines whether the Company has both (1) the power to direct the economically significant activities of the entity and (2) the obligation to absorb losses of, or the right to receive benefits from, the entity that could potentially be significant to that entity.

### ***Use of estimates***

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements.

Estimates and judgments are used in the following areas, among others: future undiscounted cash flows and subsequent fair value estimates used to assess potential and measure any impairment of long-lived assets, including goodwill and intangible assets, and the measurement of right-of-use assets and lease liabilities, contingent consideration, stock-based compensation expense, accrued expenses, income taxes, and the assessment of the Company's ability to fund its operations for at least the next twelve months from the date of issuance of these financial statements. In addition, estimates and judgments are used in the Company's accounting for its revenue-generating arrangements, in particular as it relates to determining the standalone selling price of performance obligations, evaluating whether an option to acquire additional goods and services represents a material right, estimating the total transaction price, including estimating variable consideration and the probability of achieving future potential development and regulatory milestones, assessing the period of performance over which revenue may be recognized, and accounting for modifications to revenue-generating arrangements.

[Table of Contents](#)***Foreign currency translation***

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for stockholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in stockholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations.

***Segment information***

The Company operates in a single segment, focusing on researching, developing and commercializing potentially transformative gene therapies for severe genetic diseases and cancer. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of the Company's operations are reported on a consolidated basis for purposes of segment reporting. All material long-lived assets of the Company reside in the United States.

***Cash and cash equivalents***

The Company considers all highly liquid investments purchased with original final maturities of 90 days or less from the date of purchase to be cash equivalents. Cash equivalents comprise marketable securities with maturities of less than 90 days when purchased. Cash equivalents are reported at fair value.

***Marketable securities***

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current assets. The Company's marketable securities are maintained by investment managers and consist of U.S. government agency securities and treasures, equity securities, corporate bonds, and commercial paper. Debt securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium arising at purchase is amortized to the earliest call date and any discount arising at purchase is accreted to maturity. Amortization and accretion of premiums and discounts are recorded in interest income, net. Equity securities with readily determinable fair values are also carried at fair value with unrealized gains and losses included in other (expense) income, net. Realized gains and losses on both debt and equity securities are determined using the specific identification method and are included in other (expense) income, net.

The Company classifies equity securities with readily determinable fair values, which would be available for use in its current operations, as current assets even though the Company may not dispose of such marketable securities within the next 12 months. Equity securities are included in the balance of marketable securities on the Company's consolidated balance sheet.

Effective January 1, 2020, the Company adopted ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements* ("ASU 2016-13" or "ASC 326"), using the effective date method. As the Company had never recorded any other-than-temporary-impairment adjustments to its available-for-sale debt securities prior to the effective date, no transition provisions are applicable to the Company.

The Company assesses its available-for-sale debt securities under the available-for-sale debt security impairment model in ASC 326 as of each reporting date in order to determine if a portion of any decline in fair value below carrying value recognized on its available-for-sale debt securities is the result of a credit loss. The Company records credit losses in the consolidated statements of operations and comprehensive loss as credit loss expense within other (expense) income, net, which is limited to the difference between the fair value and the amortized cost of the security. To date, the Company has not recorded any credit losses on its available-for-sale debt securities.

Accrued interest receivable related to the Company's available-for-sale debt securities is presented within receivables and other current assets on the Company's consolidated balance sheets. The Company has elected the practical expedient available to exclude accrued interest receivable from both the fair value and the amortized cost basis of available-for-sale debt securities for the purposes of identifying and measuring any impairment. The Company writes off accrued interest receivable once it has determined that the asset is not realizable. Any write offs of accrued interest receivable are recorded by reversing interest income, recognizing credit loss expense, or a combination of both. To date, the Company has not written off any accrued interest receivables associated with its marketable securities.

[Table of Contents](#)***Concentrations of credit risk and off-balance sheet risk***

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and available-for-sale securities. The Company maintains its cash and cash equivalent balances with high-quality financial institutions and, consequently, the Company believes that such funds are subject to minimal credit risk. The Company's marketable securities primarily consist of U.S. Treasury securities, U.S. government agency securities, certificates of deposit, corporate bonds, and commercial paper, and potentially subject the Company to concentrations of credit risk. The Company has adopted an investment policy that limits the amounts the Company may invest in any one type of investment and requires all investments held by the Company to be at least AA+/Aa1 rated, thereby reducing credit risk exposure.

***Fair value of financial instruments***

The Company has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements:

Level 1-Fair values are determined utilizing quoted prices (unadjusted) in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2-Fair values are determined utilizing quoted prices for identical or similar assets or liabilities in active markets or other market observable inputs such as interest rates, yield curves and foreign currency spot rates.

Level 3-Prices or valuations that require inputs that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include marketable securities (see Note 3, *Marketable securities*, and Note 4, *Fair value measurements*) and contingent consideration (see Note 4, *Fair value measurements*). The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term nature.

***Business combinations***

Business combinations are accounted for using the acquisition method of accounting. Using this method, the tangible and intangible assets acquired and the liabilities assumed are recorded as of the acquisition date at their respective fair values. The Company evaluates a business as an integrated set of activities and assets that is capable of being managed for the purpose of providing a return in the form of dividends, lower costs or other economic benefits and consists of inputs and processes that provide or have the ability to provide outputs. In an acquisition of a business, the excess of the fair value of the consideration transferred over the fair value of the net assets acquired is recorded as goodwill. In an acquisition of net assets that does not constitute a business, no goodwill is recognized.

The consolidated financial statements include the results of operations of an acquired business after the completion of the acquisition. See Note 4, *Fair value measurements*, for additional information.

***Goodwill***

Goodwill represents the excess of the purchase price over the fair value of the net assets acquired when accounted for using the acquisition method of accounting for business combinations. Goodwill is not amortized but is evaluated for impairment within the Company's single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the Company's reporting unit below its carrying amount. During the fourth quarter of 2019, the Company early adopted ASC 2017-04, *Intangibles-Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment* ("ASU 2017-04"), which removes the second step of the goodwill impairment test. Under this ASU, the Company performs a one-step quantitative test and records the amount of goodwill impairment, if any, as the excess of a reporting unit's carrying amount over its fair value, not to exceed the total amount of goodwill allocated to the reporting unit. The Company has not recognized any impairment charges related to goodwill to date.

[Table of Contents](#)***Intangible assets, net***

Intangible assets, net consist of acquired core technology and in-licensed rights with finite lives, net of accumulated amortization. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives and periodically reviews for impairment. The Company has not recognized any impairment charges related to intangible assets to date.

***Contingent consideration***

Each reporting period, the Company revalues the contingent consideration obligations associated with business combinations to their fair value and records within operating expenses increases in their fair value as contingent consideration expense and decreases in the fair value as contingent consideration income. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones may be achieved, and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as development of the Company's programs in certain indications progress and additional data are obtained, impacting the Company's assumptions. The assumptions used in estimating fair value require significant judgment. The use of different assumptions and judgments could result in a materially different estimate of fair value. See Note 4, *Fair value measurements*, for additional information.

***Property, plant and equipment***

Property, plant and equipment is stated at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Depreciation and amortization is calculated using the straight-line method over the estimated useful lives of the assets, which are as follows:

<b>Asset</b>	<b>Estimated useful life</b>
Building	40 years
Computer equipment and software	3 years
Furniture and fixtures	2-5 years
Laboratory equipment	2-5 years
Leasehold improvements	Shorter of the useful life or remaining lease term

Prior to the adoption of ASU 2016-02, *Leases (Topic 842)* ("ASU 2016-02" or "ASC 842"), on January 1, 2019 (discussed further below), the Company recorded certain costs incurred and reported by a landlord as a building asset and corresponding financing lease obligation on the consolidated balance sheets. See Note 8, *Leases*, for additional information.

***Impairment of long-lived assets***

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets.

***Leases***

Effective January 1, 2019, the Company adopted ASC 842 using the required modified retrospective approach and utilizing the effective date as its date of initial application. As a result, amounts for the year ended December 31, 2018 are presented in accordance with the previous guidance in ASC 840, *Leases* ("ASC 840").

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and current and non-current lease liabilities, as applicable. The Company does not have material financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items

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such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. To estimate its incremental borrowing rate, a credit rating applicable to the Company is estimated using a synthetic credit rating analysis since the Company does not currently have a rating agency-based credit rating. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that the Company will renew.

Assumptions made by the Company at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

*ASC 842 transition practical expedients and application of transition provisions to leases at the transition date*

The Company elected the following practical expedients, which must be elected as a package and applied consistently to all of its leases at the transition date (including those for which the entity is a lessee or a lessor): (i) the Company did not reassess whether any expired or existing contracts are or contain leases; (ii) the Company did not reassess the lease classification for any expired or existing leases (that is, all existing leases that were classified as operating leases in accordance with ASC 840 are classified as operating leases, and all existing leases that were classified as capital leases in accordance with ASC 840 are classified as finance leases); and (iii) the Company did not reassess initial direct costs for any existing leases.

For leases that existed prior to the date of initial application of ASC 842 (which were previously classified as operating leases), a lessee may elect to use either the total lease term measured at lease inception under ASC 840 or the remaining lease term as of the date of initial application of ASC 842 in determining the period for which to measure its incremental borrowing rate. In transition to ASC 842, the Company utilized the remaining lease term of its leases in determining the appropriate incremental borrowing rates.

*Application of ASC 842 policy elections to leases post adoption*

The Company has made certain policy elections to apply to its leases executed post adoption, or subsequent to January 1, 2019, as further described below.

In accordance with ASC 842, components of a lease should be split into three categories: lease components, non-lease components, and non-components. The fixed and in-substance fixed contract consideration (including any consideration related to non-components) must be allocated based on the respective relative fair values to the lease components and non-lease components.

Entities may elect not to separate lease and non-lease components. Rather, entities would account for each lease component and related non-lease component together as a single lease component. The Company has elected to account for lease and non-lease components together as a single lease component for all underlying assets and allocate all of the contract consideration to the lease component only.

ASC 842 allows for the use of judgment in determining whether the assumed lease term is for a major part of the remaining economic life of the underlying asset and whether the present value of lease payments represents substantially all of the fair value of the underlying asset. The Company applies the bright line thresholds referenced in ASC 842-10-55-2 to assist in evaluating leases for appropriate classification. The aforementioned bright lines are applied consistently to the Company's entire portfolio of leases.

[Table of Contents](#)***Revenue recognition***

Under ASC Topic 606, *Revenue from Contracts with Customers* (“Topic 606”), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer’s discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations. The identification of material rights requires judgments related to the determination of the value of the underlying good or service relative to the option exercise price. The exercise of a material right is accounted for as a contract modification for accounting purposes.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity’s promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices (“SSP”) on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company’s control or the licensee’s control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company

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recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. The Company assessed each of its revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of its arrangements.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

The Company recognizes revenue within the following financial statement captions:

#### *Service revenue*

To date, the Company's service revenue has primarily been generated from the elements of its collaboration arrangement with BMS that are accounted for pursuant to Topic 606, using the five-step model described above. As discussed further below, the Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808") or Topic 606. For the elements of a collaboration arrangement which are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606, the Company records the related revenue as service revenue on the consolidated statement of operations and comprehensive loss. Refer below for additional discussion around the Company's policy for recognizing collaborative arrangement revenue and the determination of whether elements of a collaboration arrangement are within the scope of ASC 808 or Topic 606.

#### *Collaborative arrangement revenue*

To date, the Company's collaborative arrangement revenue has been generated from its collaboration arrangements with BMS and Regeneron Pharmaceuticals, Inc. ("Regeneron"), as further described in Note 11, *Collaborative arrangements*.

The Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, which includes determining whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606 (refer above for further discussion of the Company's policy for recognizing service revenue). For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. Amounts that are owed to collaboration partners are recognized as an offset to collaborative arrangement revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed the Company's collaborative arrangement revenues in each quarterly period, such amounts are classified as research and development expense.

Prior to the adoption of *ASU No. 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606* ("ASU 2018-18") on January 1, 2020, the Company presented all revenue recognized under its collaborative arrangements as collaboration revenue on its consolidated statements of operations and comprehensive loss. However, as the Company recognizes revenue under its collaborative arrangements both within and outside the scope of Topic 606, the Company has revised its presentation of revenue on its consolidated statements of operations and comprehensive loss as follows: service revenue includes revenue from collaborative partners recognized within the scope of Topic 606 and collaborative arrangement revenue includes revenue from collaborative partners recognized outside the scope of Topic 606. The disaggregation of revenue recognized under Topic 606 and outside of Topic 606 had previously otherwise been disclosed in the notes to consolidated financial statements.

[Table of Contents](#)***Royalty and other revenue***

The Company enters into out-licensing agreements that are within the scope of Topic 606. The Company does not have any material license arrangements that contain more than one performance obligation. The terms of such out-license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of the licensor's ongoing activities, and typically include payment of one or more of the following: non-refundable up-front license fees; development and regulatory milestone payments and milestone payments based on the level of sales; and royalties on net sales of licensed products. Nonrefundable up-front license fees are recognized as revenue at a point in time when the licensed intellectual property is made available for the customer's use and benefit, which is generally at the inception of the arrangement. Development and regulatory milestone fees, which are a type of variable consideration, are recognized as revenue to the extent that it is probable that a significant reversal will not occur. The Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

For a complete discussion of accounting for collaboration and other revenue-generating arrangements, see Note 11, *Collaborative arrangements*, and Note 12, *Royalty and other revenue*.

***Research and development expenses***

Research and development costs are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, license and milestone fees, contract services, manufacturing costs for pre-launch inventory that did not qualify for capitalization, and other related costs. Up-front fees and milestones paid to third parties in connection with technologies which have not reached technological feasibility and do not have an alternative future use are expensed as research and development expense as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense. The Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants, or other clinical trial vendors that perform the activities. Where amounts owed to a collaboration partner exceed the Company's collaborative arrangement revenues in each quarterly period, such amounts are classified as research and development expense.

***Cost of royalty and other revenue***

Cost of royalty and other revenue represents expense associated with amounts owed to third parties as a result of revenue recognized under the Company's out-license arrangements.

***Stock-based compensation***

The Company's share-based compensation programs grant awards that have included stock options, restricted stock units, restricted stock awards, and shares issued under its employee stock purchase plan. Grants are awarded to employees and non-employees, including the Company's board of directors.

The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation-Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments, including grants of stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values.

The Company's stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company estimates the fair value of its option awards using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Effective January 1, 2020, the Company eliminated the use of a representative peer group and uses only its own historical volatility data in its estimate of expected volatility given that there is now a sufficient amount of historical information regarding the volatility of its own stock price. The Company has estimated the expected term of its employee stock options using the "simplified" method, whereby, the expected term equals the

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arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future.

The Company accounts for forfeitures as they occur. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Prior to the adoption of ASU No. 2018-07 on July 1, 2018, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07 on July 1, 2018, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award.

#### ***Interest income, net***

Interest income, net consists primarily of interest income earned on investments, net of amortization of premium and accretion of discount. Interest income was approximately \$11.5 million, \$34.8 million, and \$30.1 million for the years ended December 31, 2020, 2019, and 2018, respectively. Interest expense was \$0.0 million, \$0.0 million, and \$15.5 million for the years ended December 31, 2020, 2019, and 2018, respectively. Please refer to Note 8, *Leases*, for further discussion of interest expense incurred on the 60 Binney Street lease.

#### ***Other (expense) income, net***

Other (expense) income, net consists primarily of gains and losses on equity securities held by the Company, gains and losses on disposal of assets, and gains and losses on foreign currency.

#### ***Net loss per share***

Basic net loss per share is calculated by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period. Diluted net income per share is calculated by dividing the net income attributable to common stockholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options, unvested restricted stock, restricted stock units, and employee stock purchase plan stock using the treasury stock method. Given that the Company recorded a net loss for each of the periods presented, there is no difference between basic and diluted net loss per share since the effect of common stock equivalents would be anti-dilutive and are, therefore, excluded from the diluted net loss per share calculation.

The Company follows the two-class method when computing net loss per share in periods when issued shares that meet the definition of participating securities are outstanding. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to received dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders when participating securities are outstanding, losses are not allocated to the participating securities.

#### ***Income taxes***

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* (“ASC 740”), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits

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of the tax position as well as consideration of the available facts and circumstances. The Company accrues for potential interest and penalties related to unrecognized tax benefits in income tax expense.

#### ***Comprehensive loss***

Comprehensive loss is composed of net loss and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on debt securities, foreign currency translation adjustments and other items.

#### ***Recent accounting pronouncements***

*ASU No. 2016-13, Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements, ASU No. 2019-5 Financial Instruments - Credit Losses (Topic 326): Targeted Transition Relief, ASU No. 2019-11, Codification Improvements to Topic 326, Financial Instruments - Credit Losses*

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements*. The new standard, as amended, requires that expected credit losses relating to financial assets measured on an amortized cost basis and available-for-sale debt securities be recorded through an allowance for credit losses. It also limits the amount of credit losses to be recognized for available-for-sale debt securities to the amount by which carrying value exceeds fair value and also requires the reversal of previously recognized credit losses if fair value increases. The targeted transition relief standard allows filers an option to irrevocably elect the fair value option of ASC 825-10, *Financial Instruments-Overall*, applied on an instrument-by-instrument basis for eligible instruments. The Company adopted this standard on January 1, 2020 on a prospective basis and the adoption did not have a material impact on its financial position and results of operations.

*ASU No. 2018-13, Fair Value Measurement (Topic 820): Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement*

In August 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework - Changes to the Disclosure Requirements for Fair Value Measurement*. The new standard removes certain disclosures, modifies certain disclosures, and adds additional disclosures related to fair value measurement. The Company adopted this standard on January 1, 2020, and it did not have a material impact on its financial position and results of operations upon adoption.

*ASU No. 2018-15, Intangibles-Goodwill and Other - Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*

In August 2018, the FASB issued ASU 2018-15, *Intangibles-Goodwill and Other-Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract*. The amendments in this update align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use software license). The accounting for the service element of a hosting arrangement that is a service contract is not affected by the amendments in this update. The Company adopted this standard on a prospective basis as of January 1, 2020, and it did not have a material impact on its financial position and results of operations upon adoption.

*ASU No. 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*

In November 2018, the FASB issued ASU 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*, ("ASU 2018-18"). The amendments in this update clarify that certain transactions between collaborative arrangement participants should be accounted for as revenue under ASC 606, *Revenue from Contracts with Customers* ("Topic 606" or "ASC 606") when the counter party is a customer in the context of a unit of account. ASU 2018-18 also precludes companies from presenting transactions with collaborative partners that are outside the scope of Topic 606 together with revenue within the scope of Topic 606. The Company adopted this standard on a retrospective basis on January 1, 2020. As a result, revenue for prior periods are presented in accordance with the new standard.

Prior to the adoption of ASU 2018-18, the Company presented all revenue recognized under its collaborative arrangements as collaboration revenue on its consolidated statements of operations and comprehensive loss. However, as the Company recognizes revenue under its collaborative arrangements both within and outside the scope of Topic 606, the Company has revised its presentation of revenue on its consolidated statements of operations and comprehensive loss as follows: service revenue includes revenue from collaborative partners recognized within the scope of Topic 606 and collaborative arrangement revenue includes revenue from collaborative partners recognized outside the scope of Topic 606. The disaggregation of revenue

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recognized under Topic 606 and outside of Topic 606 had previously otherwise been disclosed in the notes to consolidated financial statements.

*ASU No. 2019-4, Codification Improvements to Topic 326, Financial Instruments - Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825, Financial Instruments*

In April 2019, the FASB issued ASU 2019-4, *Codification Improvements to Topic 326, Financial Instruments - Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825, Financial Instruments*. This update provides clarifications for three topics related to financial instruments accounting, some of which apply to the Company. The Company adopted this standard on January 1, 2020 on a prospective basis, and it did not have a material impact on its financial position and results of operations upon adoption.

Not yet adopted

*ASU No. 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"), which is intended to simplify the accounting for income taxes. ASU 2019-12 removes certain exceptions to the general principles in Topic 740 and also clarifies and amends existing guidance to improve consistent application. The new standard will be effective beginning January 1, 2021. The adoption of ASU 2019-12 is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

*ASU No. 2020-06, Debt-Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging-Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*

In August 2020, the FASB issued ASU 2020-06, *Debt-Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging-Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity* ("ASU 2020-06"). ASU 2020-06 simplifies the complexity associated with applying U.S. GAAP for certain financial instruments with characteristics of liabilities and equity. More specifically, the amendments focus on the guidance for convertible instruments and derivative scope exception for contracts in an entity's own equity. The Company will early adopt the new standard, effective January 1, 2021. The adoption of ASU 2020-06 is not expected to have an impact on the Company's financial position or results of operations upon adoption.

*ASU No. 2020-08, Codification Improvements to Subtopic 310-20, Receivables - Nonrefundable Fees and Other Costs*

In October 2020, the FASB issued ASU 2020-08, *Codification Improvements to Subtopic 310-20, Receivables - Nonrefundable Fees and Other Costs* ("ASU 2020-08") to provide further clarification and update the previously issued guidance in ASU 2017-08, *Receivables - Nonrefundable Fees and Other Costs (Subtopic 310-20: Premium Amortization on Purchased Callable Debt Securities)* ("ASU 2017-08"). ASU 2017-08 shortened the amortization period for certain callable debt securities purchased at a premium by requiring that the premium be amortized to the earliest call date. ASU 2020-08 requires that at each reporting period, to the extent that the amortized cost of an individual callable debt security exceeds the amount repayable by the issuer at the next call date, the excess premium shall be amortized to the next call date. The new standard will be effective beginning January 1, 2021. The adoption of ASU 2020-08 is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

*ASU No. 2020-10, Codification Improvements*

In October 2020, the FASB issued ASU 2020-10, *Codification Improvements* ("ASU 2020-10"). The amendments in this ASU represent changes to clarify the ASC, correct unintended application of the guidance, or make minor improvements to the ASC that are not expected to have a significant effect on current accounting practice or create a significant administrative cost to most entities. This new standard will be effective beginning January 1, 2021. The adoption of ASU 2020-10 is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

### 3. Marketable securities

The following table summarizes the marketable securities held at December 31, 2020 and 2019 (in thousands):

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	<b>Amortized cost / cost</b>	<b>Unrealized gains</b>	<b>Unrealized losses</b>	<b>Fair value</b>
<b>December 31, 2020</b>				
U.S. government agency securities and treasuries	\$ 675,043	\$ 302	\$ (74)	\$ 675,271
Corporate bonds	197,171	432	(40)	197,563
Commercial paper	77,949	1	-	77,950
Equity securities	20,017	-	(14,364)	5,653
Total	<b>\$ 970,180</b>	<b>\$ 735</b>	<b>\$ (14,478)</b>	<b>\$ 956,437</b>
<b>December 31, 2019</b>				
U.S. government agency securities and treasuries	\$ 633,970	\$ 2,014	\$ (48)	\$ 635,936
Certificates of deposit	960	-	-	960
Corporate bonds	185,827	824	(43)	186,608
Commercial paper	74,378	-	-	74,378
Equity securities	20,017	-	(7,147)	12,870
Total	<b>\$ 915,152</b>	<b>\$ 2,838</b>	<b>\$ (7,238)</b>	<b>\$ 910,752</b>

No available-for-sale debt securities held as of December 31, 2020 or 2019 had remaining maturities greater than five years.

[Table of Contents](#)**4. Fair value measurements**

The following table sets forth the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2020 and 2019 (in thousands):

	Total	Quoted prices in active markets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
<b>December 31, 2020</b>				
Assets:				
Cash and cash equivalents	\$ 317,705	\$ 317,705	\$ -	\$ -
Marketable securities:				
U.S. government agency securities and treasuries	675,271	-	675,271	-
Corporate bonds	197,563	-	197,563	-
Commercial paper	77,950	-	77,950	-
Equity securities	5,653	5,653	-	-
Total assets	<u>\$ 1,274,142</u>	<u>\$ 323,358</u>	<u>\$ 950,784</u>	<u>\$ -</u>
Liabilities:				
Contingent consideration	\$ 1,509	\$ -	\$ -	\$ 1,509
Total liabilities	<u>\$ 1,509</u>	<u>\$ -</u>	<u>\$ -</u>	<u>\$ 1,509</u>
<b>December 31, 2019</b>				
Assets:				
Cash and cash equivalents	\$ 327,214	\$ 311,245	\$ 15,969	\$ -
Marketable securities:				
U.S. government agency securities and treasuries	635,936	-	635,936	-
Certificates of deposit	960	-	960	-
Corporate bonds	186,608	-	186,608	-
Commercial paper	74,378	-	74,378	-
Equity securities	12,870	12,870	-	-
Total assets	<u>\$ 1,237,966</u>	<u>\$ 324,115</u>	<u>\$ 913,851</u>	<u>\$ -</u>
Liabilities:				
Contingent consideration	\$ 7,977	\$ -	\$ -	\$ 7,977
Total liabilities	<u>\$ 7,977</u>	<u>\$ -</u>	<u>\$ -</u>	<u>\$ 7,977</u>

***Cash and cash equivalents***

The Company considers all highly liquid securities with original final maturities of 90 days or less from the date of purchase to be cash equivalents. As of December 31, 2020, cash and cash equivalents comprise funds in cash and money market accounts. As of December 31, 2019, cash and cash equivalents comprise funds in cash, money market accounts, and commercial paper.

***Marketable securities***

Marketable securities classified as Level 2 within the valuation hierarchy generally consist of certificates of deposit, U.S. government agency securities and treasuries, corporate bonds, and commercial paper. The Company estimates the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources. These pricing sources utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include market pricing based on real-time trade data for the same or similar securities, issuer credit spreads, benchmark yields, and other observable inputs. The Company validates the prices provided by its third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

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The amortized cost of available-for-sale debt securities is adjusted for amortization of premiums and accretion of discounts to the earliest call date for premiums or to maturity for discounts. At December 31, 2020 and 2019, the balance in the Company's accumulated other comprehensive loss was composed primarily of activity related to the Company's available-for-sale debt securities. There were no material realized gains or losses recognized on the sale or maturity of available-for-sale securities during the year ended December 31, 2020 or 2019.

Accrued interest receivable on the Company's available-for-sale debt securities totaled \$3.1 million and \$3.6 million as of December 31, 2020 and 2019, respectively. No accrued interest receivable was written off during the twelve months ended December 31, 2020 or 2019.

The following table summarizes available-for-sale debt securities in a continuous unrealized loss position for less than and greater than twelve months, and for which an allowance for credit losses has not been recorded at December 31, 2020 and 2019 (in thousands):

Description	Less than 12 months		12 months or greater		Total	
	Fair value	Unrealized losses	Fair value	Unrealized losses	Fair value	Unrealized losses
<b>December 31, 2020</b>						
U.S. government agency securities and treasuries	\$ 211,384	\$ (74)	\$ -	\$ -	\$ 211,384	\$ (74)
Corporate bonds	76,598	(40)	1,205	-	77,803	(40)
Total	\$ 287,982	\$ (114)	\$ 1,205	\$ -	\$ 289,187	\$ (114)
<b>December 31, 2019</b>						
U.S. government agency securities and treasuries	\$ 13,234	\$ (3)	\$ 79,618	\$ (45)	\$ 92,852	\$ (48)
Corporate bonds	53,983	(43)	-	-	53,983	(43)
Total	\$ 67,217	\$ (46)	\$ 79,618	\$ (45)	\$ 146,835	\$ (91)

The Company determined that there was no material change in the credit risk of the above investments during the twelve months ended December 31, 2020. As such, an allowance for credit losses was not recognized. As of December 31, 2020, the Company does not intend to sell such securities and it is not more likely than not that the Company will be required to sell the securities before recovery of their amortized cost bases.

The Company holds equity securities with an aggregate fair value of \$5.7 million and \$12.9 million at December 31, 2020 and 2019, respectively within current marketable securities on its consolidated balance sheet. The Company recorded unrealized losses of \$7.2 million and \$9.3 million and an unrealized gain of \$2.2 million during the years ended December 31, 2020, 2019, and 2018 respectively, related to its equity securities, which are included in other (expense) income, net on the consolidated statements of operations and comprehensive loss. In January 2021, the Company sold a portion of its equity securities for proceeds of \$31.3 million. The fair value of the remaining equity securities held as of the trade date is \$7.3 million.

#### ***Contingent consideration***

In connection with its prior acquisition of Precision Genome Engineering, Inc. ("Pregenex"), the Company may be required to pay future consideration that is contingent upon the achievement of specified development, regulatory approvals or sales-based milestone events. Contingent consideration is measured at fair value and is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The valuation of contingent consideration uses assumptions the Company believes would be made by a market participant. The Company assesses these estimates on an on-going basis as additional data impacting the assumptions is obtained. Future changes in the fair value of contingent consideration related to updated assumptions and estimates are recognized within the consolidated statements of operations and comprehensive loss. In the absence of new information related to the probability of milestone achievement, changes in fair value will reflect changing discount rates and the passage of time. Contingent consideration is included in accrued expenses and other current liabilities and other non-current liabilities on the consolidated balance sheets.

Please refer to Note 9, *Commitments and contingencies*, for further information.

[Table of Contents](#)**5. Property, plant and equipment, net**

Property, plant and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2020	2019
Land	\$ 1,210	\$ 1,210
Building	15,745	15,664
Computer equipment and software	6,950	6,947
Office equipment	7,665	7,599
Laboratory equipment	55,521	44,560
Leasehold improvements	34,286	33,788
Construction-in-progress	92,514	77,981
Total property, plant and equipment	<u>213,891</u>	<u>187,749</u>
Less accumulated depreciation and amortization	(51,060)	(36,573)
Property, plant and equipment, net	<u>\$ 162,831</u>	<u>\$ 151,176</u>

Depreciation and amortization expense related to property, plant and equipment was \$15.1 million, \$13.4 million, and \$13.4 million for the years ended December 31, 2020, 2019, and 2018, respectively.

***North Carolina manufacturing facility***

In November 2017, the Company acquired a manufacturing facility in Durham, North Carolina for the future manufacture of lentiviral vector for the Company's gene therapies. As of December 31, 2020, a portion of the facility has been placed into service and the remainder of the facility is still in process of construction and qualification, which is required for the facility to be ready for its intended use. Construction-in-progress as of December 31, 2020, and 2019, includes \$91.1 million and \$74.2 million, respectively, related to the North Carolina manufacturing facility.

**6. Restricted cash**

As of both December 31, 2020 and 2019, the Company maintained letters of credit of \$54.5 million, which are collateralized with bank accounts at financial institutions in accordance with the agreements. Total restricted cash as of December 31, 2020 and 2019 consisted of the following (in thousands):

	As of December 31,	
	2020	2019
60 Binney Street lease	\$ 13,763	\$ 13,763
50 Binney Street sublease	40,072	40,072
Other	2,188	660
Total restricted cash	<u>\$ 56,023</u>	<u>\$ 54,495</u>

Refer to Note 8, *Leases*, for further information on the Company's letters of credit.

**7. Accrued expenses and other current liabilities**

Accrued expenses and other current liabilities consist of the following (in thousands):

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	As of December 31,	
	2020	2019
Employee compensation	\$ 55,802	\$ 44,679
Manufacturing costs	22,571	23,126
Clinical and contract research organization costs	23,766	16,799
Collaboration research costs	20,004	27,142
Property, plant, and equipment	789	2,354
License and milestone fees	278	300
Professional fees	1,541	1,827
Other	20,655	25,329
Total accrued expenses and other current liabilities	\$ 145,406	\$ 141,556

**8. Leases**

The Company leases certain office and laboratory space. Additionally, the Company has embedded leases at contract manufacturing organizations.

***60 Binney Street lease***

In September, 2015, the Company entered into a lease agreement for office and laboratory space located in a building (the “Building”) at 60 Binney Street, Cambridge, Massachusetts (the “60 Binney Street Lease”), which is now the Company’s corporate headquarters. Under the terms of the 60 Binney Street Lease, starting on October 1, 2016, the Company leases approximately 253,108 square feet of office and laboratory space at \$72.50 per square foot per year, or \$18.4 million per year in base rent, which is subject to scheduled annual rent increases of 1.75% plus certain operating expenses and taxes. The Company currently maintains a \$13.8 million collateralized letter of credit and, subject to the terms of the lease and certain reduction requirements specified therein, including market capitalization requirements, this amount may decrease to \$9.2 million over time. The \$13.8 million of cash collateralizing the letter of credit is classified as restricted cash and other non-current assets on the Company’s consolidated balance sheets. Pursuant to a work letter entered into in connection with the 60 Binney Street Lease, the landlord contributed an aggregate of \$42.4 million toward the cost of construction and tenant improvements for the Building.

The Company occupied the Building beginning on March 27, 2017 and the 60 Binney Street Lease will continue until March 31, 2027. The Company has the option to extend the 60 Binney Street Lease for two successive five-year terms. In applying the ASC 842 transition guidance, the Company classified this lease as an operating lease and recorded a right-of-use asset and lease liability on the effective date. The Company is recognizing rent expense on a straight-line basis throughout the remaining term of the lease.

***50 Binney Street sublease***

In April 2019, the Company entered into a sublease agreement for office space located at 50 Binney Street in Cambridge, Massachusetts (the “50 Binney Street Sublease”) to supplement the Company’s corporate headquarters located at 60 Binney Street in Cambridge, Massachusetts. Under the terms of the 50 Binney Street Sublease, the Company will lease 267,278 square feet of office space for \$99.95 per square foot, or \$26.7 million per year in base rent subject to certain operating expenses, taxes and annual rent increases of approximately 3%. The lease will commence when the space is available for use by the Company, which is anticipated to be in the first half of 2022, which reflects the sublessor’s exercise of its option to postpone the commencement date of the sublease, and end on December 31, 2030, unless other conditions specified in the 50 Binney Street Sublease occur. Upon signing the 50 Binney Street Sublease, the Company executed a \$40.1 million cash-collateralized letter of credit, which may be reduced in the future subject to the terms of the 50 Binney Street Sublease and certain reduction requirements specified therein. The \$40.1 million of cash collateralizing the letter of credit is classified as restricted cash and other non-current assets on the Company’s consolidated balance sheets. Payments will commence at the earlier of (i) the date which is 90 days following the commencement date and (ii) the date the Company takes occupancy of all or any portion of the premises. In connection with the execution of the 50 Binney Street Sublease, the Company also entered into a Purchase Agreement for furniture and equipment (the “Furniture Purchase Agreement”) located on the premises upon lease commencement. Upon execution of the Furniture Purchase Agreement, the Company made an upfront payment of \$7.5 million, all of which was recorded within restricted cash and other non-current assets on the Company’s consolidated balance sheets as

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of December 31, 2020. The Company will assess the lease classification of the 50 Binney Street Sublease and commence recognition of the associated rent expense upon lease commencement.

#### ***Seattle, Washington leases***

In July 2018, the Company entered into a lease agreement for office and laboratory space located in a portion of a building in Seattle, Washington. The lease was amended in October 2018 to increase the total rentable space to approximately 36,126 square feet at \$54.00 per square foot in base rent per year, which is subject to scheduled annual rent increases of 2.5% plus certain operating expenses and taxes. The lease commenced on January 1, 2019 and the lease term will continue through January 31, 2027 ("the Initial Term"). The Company moved into the facility in June 2019. The Company determined the classification of this lease to be an operating lease and recorded a right-of-use asset and lease liability at lease commencement.

In September 2019, the Company entered into a second amendment to the lease (the "Second Amendment"). The Second Amendment added approximately 22,188 square feet to the existing space and extended the lease term of the entire premises by 16 months, or until April 2028. Fixed monthly rent for the expanded space will be incurred at a rate of \$62.80 per square foot per year beginning in January 2021, subject to annual increases of 2.5%. The Second Amendment includes a five-year option to extend the term.

Upon the execution of the Second Amendment, which was deemed to be a lease modification, the Company re-evaluated the assumptions made at the original lease commencement date. The Company determined the Second Amendment consists of two separate contracts under ASC 842. One contract is related to a new right-of-use for the expanded 22,188 square feet of space, which is to be accounted for as a new lease, and the other is related to the modification of term for the original 36,126 square feet of space. The Company recorded an additional right-of-use asset and lease liability upon lease commencement of the expanded space. In September 2020, the Company entered into a sublease agreement for the 22,188 square feet added under the Second Amendment at a fixed monthly rent of \$62.80 per square foot per year beginning in January 2021, subject to annual increases of 2.5%. The sublease term will continue through April 2028. The Company is recognizing rent expense on a straight-line basis through the remaining extended term of the respective leases. The head lease and the sublease will be accounted for as two separate contracts with the income from the sublease presented separately from the lease expense on the head lease.

#### ***Embedded leases***

In June 2016, the Company entered into a manufacturing agreement for the future commercial production of the Company's beti-cel and eli-cel drug products with a contract manufacturing organization. Under this 12-year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, the Company paid \$12.0 million upon the achievement of certain contractual milestones. Construction was completed in March 2018 and beginning in April 2018, the Company pays \$5.1 million per year, subject to annual inflationary adjustments, in fixed suite fees, as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services. The Company may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. The Company concluded in prior periods that this agreement contained an embedded lease as the suites are designated for the Company's exclusive use during the term of the agreement. The Company recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842 and is recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In November 2016, the Company entered into an agreement for clinical and commercial production of the Company's ZYNTEGLO, LentiGlobin for SCD, and eli-cel drug products with a contract manufacturing organization at an existing facility. The Company concluded that this agreement contains an embedded operating lease as the clean rooms are designated for the Company's exclusive use during the term of the agreement. The term of the agreement is five years with subsequent three-year renewals at the mutual option of each party. As a result, the Company recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842, and is recognizing rent expense on a straight-line basis throughout the estimated remaining term of the embedded lease. In March 2020, the Company amended its agreement with the contract manufacturing organization, resulting in a lease modification. Under the terms of the amended arrangement, the Company may be required to pay annual maintenance and production fees of up to €16.5 million, depending on its production needs, and may terminate this agreement with twelve months' notice and a one-time termination fee. The amendment also provides for an option to reserve an additional clean room for a one-time option fee plus annual maintenance fees. As a result, the Company increased the right-of-use asset and lease liability related to this embedded operating lease during the first quarter of 2020.

In July 2020, the Company entered into an agreement reserving manufacturing capacity with a contract manufacturing organization. The Company concluded that this agreement contains an embedded lease as a controlled environment room at the

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facility is designated for the Company's exclusive use during the term of the agreement, with the option to sublease the space if the Company provides notice that it will not utilize it for a specified duration of time. Under the terms of the agreement, the Company will be required to pay up to \$5.4 million per year in maintenance fees in addition to the cost of any services provided and may terminate this agreement with eighteen months' notice. The term of the agreement is five years, with the option to extend, and is expected to commence in the first half of 2021. The Company intends to assess the lease classification of the embedded lease and commence recognition of the associated rent expense upon lease commencement.

***Summary of all lease costs recognized under ASC 842***

The following table contains a summary of the lease costs recognized under ASC 842 and other information pertaining to the Company's operating leases for the years ended December 31, 2020 and 2019 (in thousands):

	<b>For the year ended December 31,</b>	
	<b>2020</b>	<b>2019</b>
Lease cost <sup>(1)</sup>		
Operating lease cost	\$ 35,049	\$ 35,346
Total lease cost	<u>\$ 35,049</u>	<u>\$ 35,346</u>
Other information		
Operating cash flows used for operating leases	\$ 32,097	\$ 31,026
Weighted average remaining lease term	6.4 years	7.4 years
Weighted average discount rate	6.35%	6.70%

<sup>(1)</sup> Short-term lease costs and variable lease costs incurred by the Company for the twelve months ended December 31, 2020 and 2019 were immaterial.

Rent expense is calculated on a straight-line basis over the term of the lease. Rent expense recognized under all leases, including additional charges for utilities, parking, maintenance, and real estate taxes, was \$47.7 million, \$45.3 million, and \$9.8 million for the years ended December 31, 2020, 2019 and 2018, respectively. Note that the Company adopted ASC 842 effective January 1, 2019 using the required modified retrospective approach and utilizing the effective date as its date of initial application. Therefore, amounts disclosed pertaining to the year ended December 31, 2018 are presented under previous accounting guidance and are therefore not comparable to the amounts recorded during the years ended December 31, 2020 and 2019 under ASC 842.

As of December 31, 2020, future minimum commitments under ASC 842 under the Company's operating leases were as follows (in thousands):

<b>Maturity of lease liabilities</b>	<b>As of December 31, 2020</b>	
2021	\$ 36,430	
2022	36,899	
2023	37,387	
2024	37,398	
2025	32,082	
2026 and thereafter	56,095	
Total lease payments	236,291	
Less: imputed interest	(43,270)	
<b>Total operating lease liabilities</b>	<b>\$ 193,021</b>	

The above table excludes legally binding minimum lease payments for leases executed but not yet commenced as of December 31, 2020.

[Table of Contents](#)**9. Commitments and contingencies*****Lease commitments***

The Company leases certain office and laboratory space and has embedded leases at contract manufacturing organizations. Refer to Note 8, *Leases*, for further information on the terms of these lease agreements.

***Contingent consideration related to business combinations***

On June 30, 2014, the Company acquired Pregen. The Company may be required to make up to an additional \$120.0 million in remaining future contingent cash payments to the former equityholders of Pregen upon the achievement of certain clinical and commercial milestones related to the Pregen technology, of which \$20.1 million relates to clinical milestones and \$99.9 million relates to commercial milestones. In accordance with accounting guidance for business combinations, contingent consideration liabilities are required to be recognized on the consolidated balance sheets at fair value. Estimating the fair value of contingent consideration requires the use of significant assumptions primarily relating to probabilities of successful achievement of certain clinical and commercial milestones, the expected timing in which these milestones will be achieved and discount rates. The use of different assumptions could result in materially different estimates of fair value.

***Other funding commitments***

The Company is party to various agreements, principally relating to licensed technology, that require future payments relating to milestones that may be met in subsequent periods or royalties on future sales of specified products, which includes the collaboration agreement entered into with Regeneron in August 2018. Please refer to Note 11, *Collaborative arrangements*, for further information on the collaboration agreement with Regeneron.

Additionally, the Company is party to various contracts with contract research organizations and contract manufacturers that generally provide for termination on notice, with the exact amounts in the event of termination to be based on the timing of the termination and the terms of the agreement.

Based on our development plans as of December 31, 2020, the Company may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with the Company's collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company's financial statements. As further discussed in Note 11, *Collaborative arrangements*, BMS assumed responsibility for amounts due to licensors as a result of any future ex-U.S. sales of ide-cel and bb21217.

The Company has various manufacturing development and license agreements to support clinical and commercial product needs. The following table presents non-cancelable contractual obligations arising from these arrangements:

Years ended December 31,	Purchase commitment
2021	\$ 83,885
2022	12,611
2023	-
2024	-
2025	-
2026 and thereafter	-
Total purchase commitments	<hr/> \$ 96,496

***Litigation***

From time to time, the Company is party to various claims and complaints arising in the ordinary course of business, including securities class action litigation. The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company indemnifies, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company's business partners. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is unlimited. Management

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does not believe that any ultimate liability resulting from any of these claims will have a material adverse effect on its results of operations, financial position, or liquidity. However, management cannot give any assurance regarding the ultimate outcome of any claims, and their resolution could be material to operating results for any particular period.

The Company also indemnifies each of its directors and officers for certain events or occurrences, subject to certain limits, while the officer or director is or was serving at the Company's request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and by-laws. The term of the indemnification period lasts as long as a director may be subject to any proceeding arising out of acts or omissions of such director or officer in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company currently holds director and officer liability insurance. This insurance allows the transfer of risk associated with the Company's exposure and may enable it to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, it has not recognized any liabilities relating to these obligations.

#### **10. Common stock and preferred stock**

The Company is authorized to issue 125.0 million shares of common stock. Holders of common stock are entitled to one vote per share. Holders of common stock are entitled to receive dividends, if and when declared by the Company's board of directors, and to share ratably in the Company's assets legally available for distribution to the Company's shareholders in the event of liquidation. Holders of common stock have no preemptive, subscription, redemption or conversion rights. As of December 31, 2020, and 2019, the Company had 66.4 million and 55.4 million shares of common stock issued and outstanding, respectively.

In January 2018, the Company sold 0.3 million shares of common stock pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the December 2017 underwritten public offering at a price of \$185.00 per share for aggregate net proceeds of \$48.7 million. In July 2018, the Company sold 3.9 million shares of common stock (excluding any shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$162.50 per share for aggregate net proceeds of \$600.6 million. In August 2018, the Company sold 0.4 million shares of common stock to Regeneron in connection with a collaboration arrangement at a price of \$238.10 per share for aggregate net proceeds of \$100.0 million, of which \$45.5 million was attributed to a prepayment of joint research activities.

In May 2020, the Company sold 10.5 million shares of common stock (inclusive of shares sold pursuant to an option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of \$55.00 per share for aggregate net proceeds of \$541.5 million.

The Company is authorized to issue 5.0 million shares of preferred stock in one or more series and to fix the powers, designations, preferences and relative participating option or other rights thereof, including dividend rights, conversion rights, voting rights, redemption terms, liquidation preferences and the number of shares constituting any series, without any further vote or action by the Company's shareholders. As of December 31, 2020 and 2019, the Company had no shares of preferred stock issued or outstanding.

#### ***Reserved for future issuance***

The Company has reserved for future issuance the following number of shares of common stock (in thousands):

	As of December 31,	
	2020	2019
Options to purchase common stock	6,262	5,483
Restricted stock units	1,495	1,127
2013 Stock Option and Incentive Plan	2,545	2,007
2013 Employee Stock Purchase Plan	67	147
	<hr/> 10,369	<hr/> 8,764

[Table of Contents](#)**11. Collaborative arrangements**

To date, the Company's service and collaborative arrangement revenue has been primarily generated from its collaboration arrangements with BMS, formerly Celgene Corporation ("Celgene") prior to its acquisition by BMS in November 2019, and Regeneron, each as further described below.

**Bristol-Myers Squibb*****BMS Original Collaboration Agreement***

In March 2013, the Company entered into a Master Collaboration Agreement (the "BMS Collaboration Agreement") with Celgene (now BMS following its acquisition of Celgene in November 2019) to discover, develop and commercialize potentially disease-altering gene therapies in oncology. The collaboration is focused on applying gene therapy technology to genetically modify a patient's own T cells, known as chimeric antigen receptor, or CAR T cells, to target and destroy cancer cells. Additionally, in March 2013, the Company entered into a Platform Technology Sublicense Agreement (the "Sublicense Agreement") with BMS pursuant to which the Company obtained a sublicense to certain intellectual property from BMS, originating under BMS's license from Baylor College of Medicine, for use in the collaboration.

Under the terms of the BMS Collaboration Agreement, the Company received an up-front, non-refundable, non-creditable payment of \$75.0 million. The Company was responsible for conducting discovery, research and development activities through completion of phase 1 clinical studies, if any, during the initial term of the BMS Collaboration Agreement, or three years.

***BMS Amended Collaboration Agreement***

In June 2015, the Company and BMS amended and restated the BMS Collaboration Agreement (the "Amended BMS Collaboration Agreement"). Under the Amended BMS Collaboration Agreement, the parties narrowed the focus of the collaboration to exclusively work on anti-B-cell maturation antigen ("BCMA") product candidates for a new three-year term. In connection with the Amended BMS Collaboration Agreement, the Company received an up-front, one-time, non-refundable, non-creditable payment of \$25.0 million to fund research and development under the collaboration. Under the terms of the Amended BMS Collaboration Agreement, for up to two product candidates selected for development under the collaboration, the Company was responsible for conducting and funding all research and development activities performed up through completion of the initial phase 1 clinical study of such product candidates.

On a product candidate-by-product candidate basis, up through a specified period following enrollment of the first patient in an initial phase 1 clinical study for such product candidate, the Company had granted BMS an option to obtain an exclusive worldwide license to develop and commercialize such product. Following BMS's license of each product candidate, the Company is entitled to elect to co-develop and co-promote each product candidate in the U.S.

***BMS Ide-cel License Agreement***

In February 2016, BMS exercised its option to obtain an exclusive worldwide license to develop and commercialize ide-cel, the first product candidate under the Amended BMS Collaboration Agreement, pursuant to an executed license agreement ("Ide-cel License Agreement") entered into by the parties in February 2016 and paid to the Company the associated \$10.0 million option fee. Pursuant to the Ide-cel License Agreement, BMS was responsible for development and related funding of ide-cel after the substantial completion of the phase 1 clinical trial. The Company was responsible for the manufacture of vector and associated payload throughout development and upon BMS's request, throughout commercialization, the costs of which were reimbursable by BMS in accordance with the terms of the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement, as further described below. BMS was responsible for the manufacture of drug product throughout development and commercialization. Under the Ide-cel License Agreement, the Company was eligible to receive U.S. milestones of up to \$85.0 million for the first indication to be addressed by ide-cel and royalties for U.S. sales of ide-cel. Additionally, the Company was eligible to receive ex-U.S. milestones of up to \$55.0 million and royalties for ex-U.S. sales of ide-cel.

***BMS Ide-cel Co-Development, Co-Promote and Profit Share Agreement***

In March 2018, the Company elected to co-develop and co-promote ide-cel within the U.S. pursuant to the execution of the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement ("Ide-cel CCPS"), which replaced the Ide-cel License Agreement. As a result of executing the Ide-cel CCPS, the responsibilities of the parties remain unchanged from

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those under the Ide-cel License Agreement, however, the Company will share equally in all profits and losses relating to developing, commercializing and manufacturing ide-cel within the U.S. and has the right to participate in the development and promotion of ide-cel in the U.S. BMS is responsible for the costs incurred to manufacture vector and associated payload for use outside of the U.S., plus a markup. As a result of electing to co-develop and co-promote ide-cel within the U.S., the milestones and royalties payable under the Ide-cel License Agreement were adjusted. Under the Ide-cel CCPS, the Company was eligible to receive a \$10.0 million milestone related to the development of ide-cel in the U.S. and, for the first indication to be addressed by ide-cel, ex-U.S. regulatory and commercial milestones of up to \$60.0 million. Under the Ide-cel CCPS, the \$10.0 million development milestone was achieved in the second quarter of 2019 and subsequently paid by BMS.

In May 2020, the First Amendment to the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement (as amended, the "Amended Ide-cel CCPS") was executed, which amended the Ide-cel CCPS. Under the Amended Ide-cel CCPS, the parties will continue to share equally in all profits and losses related to developing, commercializing and manufacturing ide-cel within the U.S. Under the Amended Ide-cel CCPS and the Amended bb21217 License Agreement, described further below, BMS was relieved of its obligations to pay the Company for future ex-U.S. milestones and royalties on ex-U.S. sales for each of ide-cel and bb21217 in exchange for an up-front, non-refundable, non-creditable payment of \$200.0 million, which represents the aggregate of the probability-weighted, net present value of the future ex-U.S. milestones and royalties on ex-U.S. sales for each of ide-cel and bb21217. In connection with these amendments, BMS assumed the contract manufacturing agreements related to ide-cel adherent lentiviral vector. Over time, BMS is assuming responsibility for manufacturing ide-cel suspension lentiviral vector outside of the U.S., with bluebird responsible for manufacturing ide-cel suspension lentiviral vector in the U.S. In addition, under the Amended Ide-cel CCPS and the Amended bb21217 License Agreement, described further below, the parties are released from future exclusivity related to BCMA-directed T cell therapies. There are no remaining milestones or royalties under the Amended Ide-cel CCPS.

#### ***BMS bb21217 License Agreement***

In September 2017, BMS exercised its option to obtain an exclusive worldwide license to develop and commercialize bb21217, the second product candidate under the Amended BMS Collaboration Agreement, pursuant to an executed license agreement ("bb21217 License Agreement") entered into by the parties in September 2017 and paid the Company an option fee of \$15.0 million. Pursuant to the bb21217 License Agreement, BMS is responsible for development and related funding of bb21217 after the substantial completion of the ongoing phase 1 clinical trial. In 2019, the parties amended the protocol for the ongoing phase 1 clinical trial to enroll additional patients for which the Company will be reimbursed based upon an agreed-upon amount per patient. Under the bb21217 License Agreement, the Company is eligible to receive U.S. milestones of up to \$85.0 million for the first indication to be addressed by bb21217 and royalties for U.S. sales of bb21217. Additionally, the Company was eligible to receive ex-U.S. milestones of up to \$55.0 million and royalties for ex-U.S. sales of bb21217.

In May 2020, the Second Amended and Restated License Agreement ("Amended bb21217 License Agreement") was executed, which replaced the bb21217 License Agreement. Under the Amended bb21217 License Agreement, over time, BMS is assuming responsibility for manufacturing suspension lentiviral vector outside of the U.S., with bluebird responsible for manufacturing suspension lentiviral vector in the U.S. Under the Amended bb21217 License Agreement, expenses incurred by the Company associated with these activities are fully reimbursable by BMS at cost plus a mark-up. Throughout both development and commercialization, BMS is responsible for the manufacture of drug product. There are no remaining milestones and royalties related to the ex-U.S. development or commercialization of bb21217 following execution of the Amended bb21217 License Agreement.

The Company currently expects it will exercise its option to co-develop and co-promote bb21217 within the U.S. The Company's election to co-develop and co-promote bb21217 must be made by the substantial completion of the on-going phase 1 clinical trial of bb21217. If elected, the Company expects the responsibilities of the parties to remain largely unchanged, however, the Company expects it will share equally in all profits and losses relating to developing, commercializing and manufacturing bb21217 within the U.S. and to have the right to participate in the development and promotion of bb21217 in the U.S. Under this scenario, the U.S. milestones and royalties payable under the Amended bb21217 License Agreement would be adjusted and the Company would be eligible to receive a \$10.0 million development milestone payment related to the development of bb21217 within the U.S. The Company would not be eligible for royalties on U.S. sales of bb21217 under this scenario.

In the event the Company does not exercise its option to co-develop and co-promote bb21217, the Company will receive an additional fee in the amount of \$10.0 million. Under this scenario, there would be no change to the U.S. milestones and royalties for U.S. sales of bb21217, as previously described above, for which the Company would be eligible to receive.

[Table of Contents](#)***Accounting Analysis - Amended Ide-cel CCPS and Amended bb21217 License Agreement***

In accordance with the Company's accounting policies related to variable consideration, as further described in Note 2, *Summary of Significant Accounting Policies and Basis of Presentation*, if an arrangement includes variable consideration, including milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price of an arrangement. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received. The Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

Prior to the May 2020 amendments, the Company had constrained all variable consideration related to the remaining ex-U.S. milestones and royalties for ex-U.S. sales under the Ide-cel CCPS and bb21217 License Agreement. As a result of the May 2020 amendments, the uncertainty associated with the previously constrained variable consideration for future ex-U.S. milestones and royalties on ex-U.S. sales for each of ide-cel and bb21217 was resolved in exchange for an up-front, non-refundable, non-creditable payment of \$200.0 million.

While the Ide-cel CCPS and bb21217 License Agreement were historically accounted for as separate contracts, the May 2020 amendments to each agreement were negotiated as a package with a single commercial objective and, as such, the Amended Ide-cel CCPS and Amended bb21217 License Agreement were combined for accounting purposes and treated as a single arrangement.

At the time of the May 2020 amendments, there was one remaining performance obligation under each of the Ide-cel CCPS and bb21217 License Agreement, neither of which were fully satisfied: a combined performance obligation of the ide-cel license and ide-cel vector manufacturing through development; and a combined performance obligation of the bb21217 license and bb21217 vector manufacturing through development. Subsequent to the May 2020 amendments, the Company concluded the two performance obligations are distinct from each other as BMS can benefit from each license and associated manufacturing services separately and the respective licenses and manufacturing services do not modify one another and are not interdependent. Accordingly, the Company will continue to account for each performance obligation separately.

The Company allocated the \$200.0 million up-front payment received in connection with the May 2020 amendments to the remaining performance obligations described above based on the general allocation principles of Topic 606. In applying these principles, the Company considered the \$200.0 million up-front payment is representative of previously constrained variable consideration that has been changed and the related uncertainties resolved by the May 2020 amendments. Moreover, the Company considered that a portion of the \$200.0 million was specifically attributable to each remaining performance obligation as the amount represents the aggregate of the probability-weighted, net present value of the future ex-U.S. milestones and royalties on ex-U.S. sales for each of ide-cel and bb21217 and that each respective portion therefore (i) relates specifically to the Company's satisfaction of each of its remaining performance obligations and (ii) is representative of the amount of consideration the Company expects to be entitled to in exchange for satisfying the respective performance obligations. As such, the Company concluded that the portion of the \$200.0 million up-front payment specifically attributable to each of ide-cel and bb21217 should be allocated to each respective performance obligation pursuant to the variable consideration allocation exception.

The Amended Ide-cel CCPS and Amended bb21217 License Agreement represent a contract modification to an existing contract under Topic 606 given the May 2020 amendments resulted in a reduction in scope of the Company's responsibilities under each performance obligation described above. Specifically, the May 2020 amendments reduced the scope of the Company's obligation to provide ex-U.S. vector manufacturing services through development for both ide-cel and bb21217 as those activities will transition to BMS over time. In addition, the May 2020 amendments resulted in a change in the overall transaction price under the arrangement. The May 2020 amendments did not include any additional promised goods and services.

The remaining goods and services to be provided in order to fully satisfy each performance obligation described above are not distinct from those previously provided with respect to each performance obligation. Therefore, for each performance obligation, the remaining goods and services are part of a single performance obligation that is partially satisfied at the date of the contract modification. Accordingly, the effect that the contract modification had on the transaction price and the measure of progress toward complete satisfaction of each respective performance obligation has been recognized on a cumulative catch-up basis. The accounting for any previously satisfied performance obligations as of the contract modification date are not affected by the modification.

[Table of Contents](#)*Ide-cel transaction price*

The following tables summarize the total transaction price, the allocation of the total transaction price to the identified performance obligations under the arrangement (including those performance obligations that were completed as of the May 2020 contract modification date), and the amount of the transaction price unsatisfied as of December 31, 2020 (in thousands):

	Ide-cel transaction price as of December 31, 2020
Upfront non-refundable payments received prior to May 2020 contract modification (1)	\$ 120,000
Allocated portion of the upfront non-refundable payment received in connection with the Amended Ide-cel CCPS and bb21217 License Agreement (2)	184,029
Estimated variable consideration (3)	83,900
	<u><u>\$ 387,929</u></u>

(1) Composed of all up-front payments and option fee and milestone payments received under the BMS Collaboration Agreement, Amended BMS Collaboration Agreement, Ide-cel License Agreement, and Ide-cel CCPS. This consideration was allocated to the performance obligations under the Ide-cel CCPS based on a relative standalone selling price (“SSP”) basis. The Company estimated the SSP of the ide-cel license after considering potential future cash flows under the license. The Company then discounted these probability-weighted cash flows to their present value. The Company estimated the SSP of each of the ide-cel research and development services and ide-cel manufacturing services to be provided based on the Company’s estimated cost of providing the services plus an applicable profit margin commensurate with observable market data for similar services.

(2) This represents the portion of the \$200.0 million up-front payment received under the Amended Ide-cel CCPS and Amended bb21217 License Agreement which was allocated to ide-cel.

(3) Estimated variable consideration represents the estimated reimbursement from BMS for the manufacture of vectors and associated payload through development.

	Allocation of transaction price to performance obligations	Transaction price unsatisfied as of December 31, 2020
Ide-cel research and development services	\$ 40,912	\$ -
Ide-cel license and manufacturing services	347,017	1,082
	<u><u>\$ 387,929</u></u>	<u><u>\$ 1,082</u></u>

*Ide-cel research and development services*

The Company allocated \$40.9 million of the transaction price to the research and development services. The Company satisfied this performance obligation as the research and development services were performed. The Company determined that the period of performance of the research and development services was through projected initial phase 1 clinical study substantial completion, or through May 2018. The research and development performance obligation was satisfied prior to the May 2020 amendments and, as a result, the accounting for this previously satisfied performance obligation was not affected by the modification. The Company recognized no revenue related to ide-cel research and development services for the year ended December 31, 2020. The Company recognized \$2.3 million and \$5.8 million related to ide-cel research and development services for the year ended December 31, 2019 and 2018, respectively.

*Ide-cel license and manufacturing services*

The Company allocated \$347.0 million of the transaction price to the combined unit of accounting which consists of the license and manufacture of vectors and associated payload for incorporation into ide-cel.

The Company accounts for its vector manufacturing services for development in the U.S. and BMS’s U.S. development efforts within the scope of ASC 808 given that both parties are active participants in the activities and both parties are exposed to significant risks and rewards dependent on the commercial success of the activities. The Company recognizes collaboration revenue for its U.S. manufacturing services by analogy to Topic 606. The portion of BMS’s U.S. development costs that the Company is responsible for are recognized as a reduction to its collaboration revenues, or, if in excess of such revenues in a given quarter, the excess is recorded as research and development expense.

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The Company recognizes revenue associated with the combined performance obligation using the proportional performance method, as the Company will satisfy this performance obligation as the manufacturing services are performed through development. In using this method, the Company estimated its development plan for ide-cel, including expected demand from BMS, and the costs associated with the manufacture of vectors and associated payload for incorporation into ide-cel. On a quarterly basis, the Company determines the proportion of effort incurred as a percentage of total effort it expects to expend. This ratio is applied to the transaction price, which includes variable consideration, allocated to the combined performance obligation consisting of the ide-cel license and manufacturing services. Management has applied significant judgment in the process of developing its budget estimates and any changes to these estimates will be recognized in the period in which they change as a cumulative catch-up.

The following table summarizes the net collaboration revenue or expense incurred for the joint ide-cel development efforts in the U.S. under ASC 808, including revenue or expense related to the combined performance obligation for the license and vector manufacturing of ide-cel in the U.S. for the years ended December 31, 2020, 2019, and 2018 (in thousands):

	For the years ended December 31,		
	2020	2019	2018
ASC 808 ide-cel license and manufacturing revenue - U.S. <sup>(1)</sup>	\$ 108,196	\$ -	\$ 6,255
ASC 808 ide-cel research and development expense - U.S. <sup>(1)</sup>	\$ 41,599	\$ 32,415	\$ 8,689

<sup>(1)</sup>As noted above, the calculation of collaboration revenue or research and development expense to be recognized for joint ide-cel development efforts in the U.S. is performed on a quarterly basis. The calculation is independent of previous activity, which may result in fluctuations between revenue and expense recognition period over period, depending on the varying extent of effort performed by each party during the period.

Revenue related to the combined unit of accounting for the non-US license and vector manufacturing services is accounted for in accordance with Topic 606. The following table summarizes the revenue recognized related to the combined unit of accounting for the ide-cel ex-U.S. license and vector manufacturing services for the years ended December 31, 2020, 2019, and 2018 (in thousands):

	For the years ended December 31		
	2020	2019	2018
ASC 606 ide-cel license and manufacturing revenue - ex-U.S.	\$ 99,053	\$ 25,522	\$ 35,900

As of December 31, 2020, the aggregate amount of the transaction price allocated to the combined performance obligation, which consists of the ide-cel license and manufacturing services, that is unsatisfied, or partially unsatisfied, is \$1.1 million, which the Company expects to recognize as revenue as manufacturing services are provided through the remaining development period. As of December 31, 2020 and 2019, the Company had \$0.8 million and \$8.5 million, respectively, of deferred revenue associated with the combined performance obligation consisting of the ide-cel license and manufacturing services.

*bb21217 transaction price*

The following tables summarize the total transaction price, the allocation of the total transaction price to the identified performance obligations under the arrangement (including those performance obligations that were completed as of the May 2020 contract modification date), and the amount of the transaction price unsatisfied as of December 31, 2020 (in thousands):

(in thousands)	bb21217 transaction price as of December 31, 2020
Upfront non-refundable payments received prior to May 2020 contract modification (1)	\$ 15,000
Allocated portion of the up-front non-refundable payment received in connection with the Amended Ide-cel CCPS and bb21217 License Agreement (2)	15,971
Estimated variable consideration (3)	1,803
	<u><u>\$ 32,774</u></u>

(1) Composed of the up-front non-refundable payment received under the bb21217 License Agreement. This consideration was allocated to the performance obligations under the bb21217 License Agreement based on a relative SSP basis. The Company estimated the SSP of the bb21217 license after considering potential future cash flows under the license. The

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Company then discounted these probability-weighted cash flows to their present value. The Company estimated the SSP of each of the bb21217 research and development services and bb21217 manufacturing services to be provided based on the Company's estimated cost of providing the services plus an applicable profit margin commensurate with observable market data for similar services.

(2) This represents the portion of the \$200.0 million up-front payment received under the Amended Ide-cel CCPS and Amended bb21217 License Agreement which was allocated to bb21217.

(3) Estimated variable consideration represents the estimated reimbursement from BMS for the manufacture of vectors and associated payload through development.

	Allocation of transaction price to performance obligations	Transaction price unsatisfied as of December 31, 2020
bb21217 research and development services	\$ 5,444	\$ -
bb21217 license and manufacturing services	27,330	27,330
	<u><u>\$ 32,774</u></u>	<u><u>\$ 27,330</u></u>

All of the remaining development, regulatory, and commercial milestones under the Amended bb21217 License Agreement are related to U.S. development, regulatory and commercialization activities and are fully constrained and are therefore excluded from the transaction price. As part of its evaluation of the constraint, the Company considered numerous factors, including the fact that achievement of the milestones is outside the control of the Company and contingent upon the future success of its clinical trials, the licensee's efforts, or the receipt of regulatory approval. Any consideration related to U.S. sales-based milestones (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to BMS and therefore are recognized at the later of when the performance obligation is satisfied, or the related sales occur.

The Company re-evaluates the transaction price, including its estimated variable consideration included in the transaction price and all constrained amounts, each reporting period and as uncertain events are resolved or other changes in circumstances occur.

#### *bb21217 research and development services*

The Company satisfied this performance obligation as the research and development services were performed. The Company determined that the period of performance of the research and development services was two years through projected substantial completion of the initial phase 1 clinical study, or through September 2019. The research and development performance obligation was satisfied prior to the May 2020 amendments, and as a result, the accounting for this previously satisfied performance obligation was not affected by the modification. As part of performing its initial obligation to complete a phase 1 trial as originally contemplated, the Company recognized no revenue for the year ended December 31, 2020 and revenue of \$2.2 million and \$2.9 million for the years ended December 31, 2019 and 2018, respectively.

The agreement to expand the bb21217 phase 1 trial that occurred in 2019 was previously treated as a separate contract for accounting purposes, because the trial expansion was for the addition of a promised good or service that is distinct and the associated consideration reflected the standalone selling price of the additional promised good or service. This contract was not affected by the May 2020 amendments and, accordingly, the accounting for this agreement was not impacted by the May 2020 amendments. The transaction price associated with these additional patients consists of variable consideration and is based upon an agreed-upon amount per patient which will be recognized as revenue as the patients are treated. The Company began fulfilling the performance obligation in the fourth quarter of 2019 and it was satisfied in the fourth quarter of 2020. In connection with treating additional patients in the phase 1 trial, the Company recognized revenue of \$12.4 million, \$0.4 million, and \$0.0 million for the years ended December 31, 2020, 2019, and 2018, respectively.

#### *bb21217 license and manufacturing services*

The Company will satisfy its performance obligation related to the manufacture of vectors and associated payload for incorporation into bb21217 through development as the bb21217 manufacturing services are performed. As of December 31, 2020, the manufacturing services for bb21217 had not yet commenced. Therefore, no amounts have been recognized for the combined performance obligation in the consolidated statements of operations and comprehensive loss for the years ended December 31, 2020, 2019, and 2018.

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The aggregate amount of the transaction price allocated to the combined performance obligation, which consists of the bb21217 license and manufacturing services, is \$27.3 million. The Company does not expect that recognition will begin in the next twelve months and has therefore classified deferred revenue associated with the combined performance obligation as deferred revenue, net of current portion on its consolidated balance sheet. The Company had \$25.8 million and \$9.8 million of remaining deferred revenue as of December 31, 2020 and 2019, respectively, associated with the combined performance obligation consisting of the bb21217 license and manufacturing services.

*Contract assets and liabilities - ide-cel and bb21217*

The Company receives payments from its collaborative partners based on billing schedules established in each contract. Up-front payments and fees are recorded as deferred revenue upon receipt or when due until such time as the Company satisfies its performance obligations under these arrangements. A contract asset is a conditional right to consideration in exchange for goods or services that the Company has transferred to a customer. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional.

The following table presents changes in the balances of the Company's BMS receivables and contract liabilities during the twelve months ended December 31, 2020 (in thousands):

	Balance at December 31, 2019	Additions	Deductions	Balance at December 31, 2020
Receivables	\$ 400	\$ 12,400	\$ (12,400)	\$ 400
Contract liabilities:				
Deferred revenue	\$ 18,265	\$ 200,000	\$ (191,683)	\$ 26,582

The change in the receivables balance for the year ended December 31, 2020 is primarily driven by amounts owed to the Company for bb21217 research and development services provided during the period (expanded phase 1 clinical trial), offset by amounts collected from BMS in the period.

The increase in deferred revenue during the year ended December 31, 2020 is primarily driven by the \$200.0 million consideration received in connection with the May 2020 amendments, offset by revenue recognized in the year-to-date period related to the combined unit of accounting for ide-cel license and vector manufacturing services. A total of \$191.7 million was released from deferred revenue during the year-to-date period, of which \$169.2 million is related to a cumulative catch-up adjustment to revenue recorded in connection with the May 2020 contract modification described further above. As of December 31, 2019, the Company had \$8.5 million of deferred revenue associated with the combined performance obligation consisting of the ide-cel license and manufacturing services, of which \$8.2 million was released during the year ended December 31, 2020.

**Regeneron**

***Regeneron Collaboration Agreement***

In August 2018, the Company entered into a Collaboration Agreement (the "Regeneron Collaboration Agreement") with Regeneron pursuant to which the parties will apply their respective technology platforms to the discovery, development, and commercialization of novel immune cell therapies for cancer. In August 2018, following the completion of required regulatory reviews, the Regeneron Collaboration Agreement became effective. Under the terms of the agreement, the parties will leverage Regeneron's proprietary platform technologies for the discovery and characterization of fully human antibodies, as well as T cell receptors directed against tumor-specific proteins and peptides and the Company will contribute its field-leading expertise in gene therapy.

In accordance with the Regeneron Collaboration Agreement, the parties jointly selected six initial targets and intend to equally share the costs of research up to the point of submitting an IND application for a potential gene therapy product directed to a particular target. Additional targets may be selected to add to or replace any of the initial targets during the five-year research collaboration term as agreed to by the parties.

Regeneron will accrue a certain number of option rights exercisable against targets as the parties reach certain milestones under the terms of the agreement. Upon the acceptance of an IND for the first product candidate directed to a target, Regeneron will have the right to exercise an option for co-development/co-commercialization of product candidates directed to such target.

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on a worldwide or applicable opt-in territory basis, with certain exceptions. Where Regeneron chooses to opt-in, the parties will share equally in the costs of development and commercialization, and will share equally in any profits or losses therefrom in applicable opt-in territories. Outside of the applicable opt-in territories, the target becomes a licensed target and Regeneron would be eligible to receive, with respect to any resulting product, milestone payments of up to \$130.0 million per product and royalties on net sales outside of the applicable opt-in territories at a rate ranging from the mid-single digits to low-double digits. A target would also become a licensed target in the event Regeneron does not have an option to such target, or Regeneron does not exercise its option with respect to such target.

Either party may terminate a given research program directed to a particular target for convenience, and the other party may elect to continue such research program at its expense, receiving applicable cross-licenses. The terminating party will receive licensed product royalties and milestone payments on the potential applicable gene therapy products. Where the Company terminates a given research program for convenience, and Regeneron elects to continue such research program, the parties will enter into a transitional services agreement. Under certain conditions, following its opt-in, Regeneron may terminate a given collaboration program and the Company may elect to continue the development and commercialization of the applicable potential gene therapy products as licensed products.

#### ***Regeneron Share Purchase Agreement***

A Share Purchase Agreement (“SPA”) was entered into by the parties in August 2018. In August 2018, on the closing date of the transaction, the Company issued Regeneron 0.4 million shares of the Company’s common stock, subject to certain restrictions, for \$238.10 per share, or \$100.0 million in the aggregate. The purchase price represents \$63.0 million worth of common stock plus a \$37.0 million premium, which represents a collaboration research advancement, or credit to be applied to Regeneron’s initial 50 percent funding obligation for collaboration research, after which the collaborators will continue to fund ongoing research equally. The collaboration research advancement only applies to pre-IND research activities and is not refundable or creditable against post-IND research activities for any programs where Regeneron exercises their opt-in rights.

#### ***Accounting analysis - Regeneron***

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 0.4 million shares of the Company’s common stock and joint research activities during the five year research collaboration term. The Company determined the total transaction price to be \$100.0 million, which comprises \$54.5 million attributed to the equity sold to Regeneron and \$45.5 million attributed to the joint research activities. In determining the fair value of the common stock at closing, the Company considered the closing price of the common stock on the closing date of the transaction and included a lack of marketability discount because Regeneron received shares subject to certain restrictions.

The Company analyzed the joint research activities to assess whether they fall within the scope of ASC 808, and will reassess this throughout the life of the arrangement based on changes in the roles and responsibilities of the parties. Based on the terms of the arrangement as outlined above, for the collaboration research performed prior to submission of an IND application for a potential gene therapy product, both parties are deemed to be active participants in the collaboration. Both parties are performing research and development activities and will share equally in these costs through IND. Additionally, Regeneron and the Company are exposed to significant risks and rewards dependent on the commercial success of any product candidates that may result from the collaboration. As such, the collaboration arrangement is deemed to be within the scope of ASC 808.

The \$45.5 million attributed to the joint research activities includes the \$37.0 million creditable against amounts owed to the Company by Regeneron. The collaboration research advancement will be reduced over time for amounts due to the Company by Regeneron as a result of the parties agreeing to share in the costs of collaboration research equally. The remainder of the amount attributed to the joint research activities will be recognized over the five-year research collaboration term.

Consistent with its collaboration accounting policy, the Company will recognize collaboration revenue or research and development expense related to the joint research activities in future periods depending on the amounts incurred by each party in a given reporting period. That is, if the Company’s research costs incurred exceed those research costs incurred by Regeneron in a given quarter, the Company will record collaboration revenue and reduce the original \$37.0 million advance by the amount due from Regeneron until such advancement is fully utilized, after which the Company would record an amount due from Regeneron. If Regeneron’s research costs incurred exceed those research costs incurred by the Company in a given quarter, the Company will record research and development expense and record a liability for the amount due to Regeneron. As of December 31, 2020 and 2019, the Company has \$30.8 million and \$38.2 million, respectively, of the amount attributed to the joint research activities remaining to be recognized which is classified as collaboration research advancement, current portion and collaboration research advancement, net of current portion on the consolidated balance sheet.

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The Company recognized \$7.4 million and \$5.7 million of collaboration revenue from the Regeneron Collaboration Agreement during the years ended December 31, 2020 and 2019, respectively.

## **12. Royalty and other revenue**

### **Novartis Pharma AG**

In April 2017, the Company entered into a worldwide license agreement with Novartis. Under the terms of the agreement, Novartis non-exclusively licensed certain patent rights related to lentiviral vector technology to develop and commercialize CAR T cell therapies for oncology, including Kymriah (formerly known as CTL19), Novartis's anti-CD19 CAR T therapy. At contract inception, financial terms of the agreement included a \$7.5 million payment upon execution, \$7.5 million of potential future milestone payments associated with regulatory approvals, and \$1.1 million of payments for each subsequently licensed product, as well as low single digit royalty payments on net sales of covered products. In August 2017, Novartis received FDA approval for Kymriah and paid the Company \$2.5 million as a result of the achievement of a related milestone.

Under Topic 606, the Company identified only one performance obligation, consisting of the license, which was satisfied at contract inception. Accordingly, the nonrefundable license fee of \$7.5 million was recognized as revenue upon contract execution in the second quarter of 2017 and a \$2.5 million regulatory milestone was recognized as revenue upon milestone achievement, also in the second quarter of 2017, given there were no other unsatisfied performance obligations in the arrangement. Regulatory approvals are not within the Company's control or the licensee's control and are generally not considered probable of being achieved until those approvals are received. As such, these milestones are constrained until such time as regulatory approvals are received. Because the single performance obligation was previously satisfied, all regulatory milestones will be recognized as revenue in full in the period in which the associated milestone is achieved.

The Company began recognizing royalty revenue from sales of Kymriah in the fourth quarter of 2017. As the license was deemed to be the predominant item to which the royalties relate, the Company recognizes royalties from the sales of Kymriah when the related sales occur. For the years ended December 31, 2020, 2019, and 2018, the Company recognized royalty and other revenue of \$21.1 million, \$8.2 million, and \$2.2 million, respectively. For the years ended December 31, 2020, 2019, and 2018, the Company recognized cost of royalty and other revenue of \$54 million, \$3.0 million, and \$0.9 million, respectively.

In December 2020, the Company received notice of termination from Novartis for the license agreement described above. This termination will be effective in March 2021, at which point in time Novartis will no longer be required to pay the Company royalty or other payments on net sales of Kymriah or any future products.

### **Orchard Therapeutics Limited (assigned by GlaxoSmithKline Intellectual Property Development Limited)**

In April 2017, the Company entered into a worldwide license agreement with GlaxoSmithKline Intellectual Property Development Limited ("GSK"). Under the terms of the agreement, GSK non-exclusively licensed certain patent rights related to lentiviral vector technology to develop and commercialize gene therapies for Wiscott-Aldrich syndrome and metachromatic leukodystrophy, two rare genetic diseases. Financial terms of the agreement include a nonrefundable upfront payment of \$3.0 million as well as \$1.3 million of potential milestone payments related to each marketing authorization for each indication in any country as well as low single digit royalties on net sales of covered products. This license agreement was assigned by GSK to Orchard Therapeutics Limited, effective in April 2018.

Under Topic 606, the Company identified only one performance obligation, consisting of the license, which was satisfied at contract inception. Accordingly, the entire nonrefundable license fee of \$3.0 million was recognized as revenue upon contract execution in the second quarter of 2017 given there were no other unsatisfied performance obligations in the arrangement. Regulatory approvals are not within the Company's control or the licensee's control and are generally not considered probable of being achieved until those approvals are received. As such, these milestones are constrained until such time as after regulatory approvals are received. There was no revenue recognized under this arrangement in the years ended December 31, 2020, 2019, or 2018. Because the single performance obligation was previously satisfied, all regulatory milestones will be recognized as revenue in full in the period in which the associated milestone is achieved.

Given there was no revenue recognized under this arrangement in the years ended December 31, 2020, 2019, or 2018, there was no associated cost of royalty and other revenue.

## **13. Intangible assets**

Intangible assets, net of accumulated amortization, are summarized as follows (in thousands):

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	As of December 31,			As of December 31,		
	2020			2019		
	Cost	Accumulated amortization	Net	Cost	Accumulated amortization	Net
Developed technology	\$ 30,100	\$ (24,456)	\$ 5,644	\$ 30,100	\$ (20,694)	\$ 9,406
In-licensed rights	5,224	(827)	4,397	5,224	(304)	4,920
Total	\$ 35,324	\$ (25,283)	\$ 10,041	\$ 35,324	\$ (20,998)	\$ 14,326

Amortization expense for intangible assets was \$4.3 million, \$4.1 million, and \$3.8 million for each of the years ended December 31, 2020, 2019 and 2018, respectively.

#### ***Developed technology***

The Company's developed technology was obtained through its acquisition of Pregenex, a privately-held biotechnology company in 2014. The Company obtained gene editing and cell signaling technology with a broad range of potential therapeutic applications. The Company considered the intangible asset acquired to be developed technology, as at the date of the acquisition it could be used the way it was intended to be used in certain ongoing research and development activities. The gene editing platform intangible asset is being amortized on a straight-line basis over its expected useful life of approximately eight years from the date of the acquisition. Please refer to Note 4, *Fair value measurements*, and Note 9, *Commitments and contingencies*, for further information.

#### ***In-licensed rights***

In-licensed rights consist of capitalized milestone payments made to third parties upon receiving regulatory approval of ZYNTEGLO in the EU. The in-licensed rights are being amortized on a straight-line basis over the remaining life of the related patents of approximately ten years, as the life of the related patents reflects the expected time period that the Company will benefit from the in-licensed rights.

The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (in thousands):

	As of December 31, 2020
2021	\$ 4,285
2022	2,404
2023	522
2024	522
2025	522
2026 and thereafter	1,786
Total	<u>\$ 10,041</u>

#### **14. Stock-based compensation**

In June 2013, the Company's board of directors adopted its 2013 Stock Option and Incentive Plan ("2013 Plan"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO. The 2013 Plan replaces the 2010 Stock Option and Grant Plan ("2010 Plan").

The 2013 Plan allows for the granting of incentive stock options, non-qualified stock options, restricted stock units and restricted stock awards to the Company's employees, members of the board of directors, and consultants of the Company. The Company initially reserved 1.0 million shares of its common stock for the issuance of awards under the 2013 Plan. The 2013 Plan provides that the number of shares reserved and available for issuance under the 2013 Plan will automatically increase each January 1, beginning on January 1, 2014, by four percent of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Company's compensation committee. In January 2020 and January 2021, the number of common stock available for issuance under the 2013 Plan was increased by approximately 2.2 million and 2.7 million shares, respectively, as a result of this automatic increase provision.

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Any options or awards outstanding under the Company's previous stock option plans, including both the 2010 Plan and the Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan ("2002 Plan"), at the time of adoption of the 2013 Plan remain outstanding and effective. The shares of common stock underlying any awards that are forfeited, canceled, repurchased, expired or are otherwise terminated (other than by exercise) under the 2002 Plan and 2010 Plan are added to the shares of common stock available for issuance under the 2013 Plan. As of December 31, 2020, the total number of common stock that may be issued under all plans is 2.6 million.

The Company does not currently hold any treasury shares. Upon stock option exercise, the Company issues new shares and delivers them to the participant.

#### ***Stock-based compensation expense***

The Company recognized stock-based compensation expense totaling \$156.6 million, \$160.6 million, and \$110.8 million during the years ended December 31, 2020, 2019 and 2018, respectively. Stock-based compensation expense recognized by award type is as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Stock options	\$ 93,977	\$ 95,668	\$ 83,449
Restricted stock units	49,326	63,580	26,628
Employee stock purchase plan and other	13,328	1,381	759
	<u>\$ 156,631</u>	<u>\$ 160,629</u>	<u>\$ 110,836</u>

Stock-based compensation expense by classification included within the consolidated statements of operations and comprehensive loss was as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Research and development	\$ 72,239	\$ 80,139	\$ 54,422
Selling, general and administrative	84,392	80,490	56,414
	<u>\$ 156,631</u>	<u>\$ 160,629</u>	<u>\$ 110,836</u>

In February 2018, the Company issued restricted stock units with service and performance conditions to employees, less than 0.1 million of which are outstanding as of December 31, 2020. Vesting of these awards is contingent on the occurrence of a certain regulatory milestone event which was achieved in June 2019 and fulfillment of any remaining service condition. The Company began recognizing expense for these awards in the second quarter of 2019 when achievement of the regulatory milestone was deemed probable. The Company recognized \$20.1 million of expense related to these awards in the second quarter of 2019 and will continue to recognize stock-based compensation expense related to these awards through June 2021 when the final tranche of the awards vest.

As of December 31, 2020, the Company had \$146.0 million, \$89.3 million and \$0.4 million of unrecognized compensation expense related to unvested stock options, restricted stock units (exclusive of those with service and performance conditions that have not yet been achieved) and the employee stock purchase plan, respectively, that is expected to be recognized over a weighted-average period of 2.1 years, 2.4 years, and 0.3 years, respectively.

#### ***Stock options***

The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2020	2019	2018
Expected volatility	69.5%	70.7%	75.5%
Expected term (in years)	6.0	6.0	6.0
Risk-free interest rate	1.4%	2.3%	2.7%
Expected dividend yield	0.0%	0.0%	0.0%

The following table summarizes the stock option activity under the Company's equity awards plans:

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	<u>Shares (in thousands)</u>	<u>Weighted-average exercise price per share</u>	<u>Weighted-average contractual life (in years)</u>	<u>Aggregate intrinsic value (a) (in thousands)</u>
Outstanding at December 31, 2019	5,483	\$ 116.30		
Granted	1,585	\$ 69.40		
Exercised	(95)	\$ 19.43		
Canceled or forfeited	(711)	\$ 124.00		
Outstanding at December 31, 2020	<u>6,262</u>	<u>\$ 105.02</u>	<u>7.0</u>	<u>\$ 15,716</u>
Exercisable at December 31, 2020	<u>3,669</u>	<u>\$ 107.11</u>	<u>5.8</u>	<u>\$ 15,659</u>
Vested and expected to vest at December 31, 2020	<u>6,262</u>	<u>\$ 105.02</u>	<u>7.0</u>	<u>\$ 15,716</u>

(a)The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of the common stock for the options that were in the money at December 31, 2020.

The weighted-average fair values of options granted during 2020, 2019 and 2018 was \$43.24, \$83.44, and \$125.12, respectively. The intrinsic value of options exercised during the years ended December 31, 2020, 2019, and 2018, was \$4.0 million, \$29.0 million and \$73.1 million, respectively.

#### **Restricted stock units**

The following table summarizes the restricted stock unit activity under the Company's equity award plans:

	<u>Shares (in thousands)</u>	<u>Weighted-average grant date fair value</u>
Unvested balance at December 31, 2019	1,127	\$ 146.10
Granted	1,018	70.18
Vested	(433)	130.10
Forfeited	(217)	123.32
Unvested balance at December 31, 2020	<u>1,495</u>	<u>\$ 102.34</u>

The intrinsic value of restricted stock units vested during the years ended December 31, 2020, 2019, and 2018 was \$30.9 million, \$28.4 million and \$25.5 million, respectively.

#### **Employee Stock Purchase Plan**

In June 2013, the Company's board of directors adopted its 2013 Employee Stock Purchase Plan ("2013 ESPP"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO. The 2013 ESPP authorizes the initial issuance of up to a total of 0.2 million shares of the Company's common stock to participating employees. During each of the years ended December 31, 2020 and 2019, less than 0.1 million shares of common stock were issued under the 2013 ESPP, respectively.

#### **15. 401(k) Savings plan**

In 1997, the Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code ("the 401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. In March 2021, the Company expects to make matching contributions of approximately \$5.2 million related to employee contributions made during 2020. In March 2020, the Company made \$4.6 million of matching contributions related to employee contributions made during 2019. The match contribution is included in accrued expenses and other current liabilities as of December 31, 2020 and 2019. Expense related to the 401(k) Plan totaled \$5.2 million, \$4.6 million, \$2.4 million for the years ended December 31, 2020, 2019, and 2018, respectively.

#### **16. Income taxes**

The components of loss before income taxes were as follows (in thousands):

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	Year ended December 31,		
	2020	2019	2018
U.S.	\$ (489,091)	\$ (649,172)	\$ (440,473)
Foreign	(128,918)	(140,981)	(114,965)
Total	<u>\$ (618,009)</u>	<u>\$ (790,153)</u>	<u>\$ (555,438)</u>

The provision for (benefit from) income taxes were as follows (in thousands):

	Year ended December 31,		
	2020	2019	2018
Current:			
Federal	\$ -	\$ -	\$ -
State	2	7	324
Foreign	684	612	222
Deferred:			
Federal	-	(966)	(307)
State	-	(198)	(52)
Foreign	-	-	-
Total income tax expense (benefit)	<u>\$ 686</u>	<u>\$ (545)</u>	<u>\$ 187</u>

A reconciliation of income tax expense (benefit) computed at the statutory federal income tax rate to the Company's effective income tax rate as reflected in the financial statements is as follows:

	Year ended December 31,		
	2020	2019	2018
Federal income tax expense at statutory rate	21.0%	21.0%	21.0%
State income tax, net of federal benefit	3.1%	3.7%	5.1%
Permanent differences	(0.6)%	(0.8)%	(0.7)%
Stock-based compensation	(2.4)%	(0.7)%	1.6%
Research and development credit	6.0%	5.4%	6.5%
Foreign differential	(4.6)%	(3.7)%	(4.4)%
Federal tax rate change	-%	-%	0.1%
Other	(0.3)%	0.8%	(0.1)%
Change in valuation allowance	(22.3)%	(25.6)%	(29.1)%
Effective income tax rate (expense) benefit	(0.1)%	0.1%	-%

For the years ended December 31, 2020, 2019 and 2018, the Company recognized an income tax expense (benefit) of \$0.7 million or (0.1)%, \$(0.5) million or 0.1%, and \$0.2 million or 0.0%, respectively. The Company did not recognize any significant tax expense for the years ended December 31, 2020, 2019, or 2018 as the Company was subject to a full valuation allowance.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets and liabilities are composed of the following (in thousands):

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	Year ended December 31,	
	2020	2019
<b>Deferred tax assets:</b>		
U.S. net operating loss carryforwards (federal and state)	\$ 546,098	\$ 439,839
Tax credit carryforwards (federal and state)	246,742	213,810
Capitalized license fees and research and development expenses	14,402	16,295
Deferred revenue	15,644	15,119
Stock-based compensation	51,828	46,111
Lease liabilities	48,680	52,631
Accruals and other	14,536	15,432
Total deferred tax assets	<u>937,930</u>	<u>799,237</u>
Intangible assets	(1,499)	(2,518)
Right-of-use assets	(45,976)	(49,480)
Fixed assets	(7,576)	(2,670)
Less valuation allowance	<u>(882,879)</u>	<u>(744,569)</u>
Net deferred taxes	<u>\$ -</u>	<u>\$ -</u>

A valuation allowance is recorded against deferred tax assets if it is more likely than not that some or all of the deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future tax returns, the Company has recorded a full valuation allowance against the Company's otherwise recognizable net deferred tax assets. The valuation allowance increased on a net basis by approximately \$138.3 million during the year ended December 31, 2020 due primarily to net operating losses, tax credit carryforwards, and stock-based compensation. Effective January 1, 2019, the Company adopted ASU 2016-02, which resulted in the de-recognition of the 60 Binney Street lease and related fixed assets and the recognition of lease liabilities and right-of-use assets. The Company adjusted its deferred tax balances as a result of the adoption.

As of December 31, 2020, 2019 and 2018, the Company had U.S. federal net operating loss carryforwards of approximately \$2.03 billion, \$1.62 billion, and \$1.10 billion, respectively, which may be available to offset future income tax liabilities. Of the amount as of December 31, 2020, \$1.32 billion will carryforward indefinitely while \$711.0 million will expire at various dates through 2037. As of December 31, 2020, 2019 and 2018, the Company also had U.S. state net operating loss carryforwards of approximately \$1.89 billion, \$1.56 billion, and \$1.08 billion, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2039.

As of December 31, 2020, 2019 and 2018, the Company had federal research and development and orphan drug tax credit carryforwards of approximately \$235.3 million, \$203.1 million, and \$156.2 million, respectively, available to reduce future tax liabilities which expire at various dates through 2039. As of December 31, 2020, 2019 and 2018, the Company had state credit carryforwards of approximately \$14.5 million, \$13.6 million, and \$14.3 million, respectively, available to reduce future tax liabilities which expire at various dates through 2034. During the fourth quarter of 2018, the Company completed an analysis of prior year estimates of U.S. research and development and orphan drug tax credits for the years 2013 through 2017. The analysis resulted in an immaterial adjustment to the Company's income tax benefit, which was offset by an adjustment to the valuation allowance. An analysis of the U.S. research and development and orphan drug credits has not yet been completed for 2018, 2019, or 2020.

In March 2020, the Coronavirus Aid, Relief and Economic Security Act ("CARES Act") was enacted. This law temporarily suspends and adjusts certain law changes enacted in the Tax Cuts and Jobs Act in 2017. In December 2020, the Consolidated Appropriations Act was enacted. This law modified the employee retention credit under the CARES Act and created credit extenders for certain credits. The Company has concluded that the provisions in the CARES Act and Consolidated Appropriations Act have an immaterial impact on the Company's income tax expense due to its cumulative losses and full valuation allowance position.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be

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utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception and prior to its initial public offering in 2013, which it believes has resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code. The Company completed a study through September 2019 confirming no ownership changes have occurred since the Company's initial public offering in 2013; any ownership shifts occurring after September 2019 could result in an ownership change under Section 382.

The Company files Federal income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2017 through December 31, 2019. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, or state or foreign tax authorities to the extent utilized in a future period.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	Unrecognized tax benefits
Balance as of December 31, 2018	\$ 12,095
Increases (decreases) for tax positions related to current period	3,554
Increases (decreases) for tax positions related to prior periods	296
Balance as of December 31, 2019	<u>15,945</u>
Increases (decreases) for tax positions related to current period	3,149
Increases (decreases) for tax positions related to prior periods	(100)
Balance as of December 31, 2020	<u>18,994</u>

The unrecognized tax benefits at December 31, 2020, if recognized, would not affect the Company's effective tax rate due to its full valuation allowance position. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease within the next 12 months. The Company has elected to include interest and penalties related to uncertain tax positions as a component of its provision for income taxes. For the years ended December 31, 2020, 2019 and 2018, the Company's accrued interest and penalties related to uncertain tax positions were not material.

#### 17. Net loss per share

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect (in thousands):

	Year ended December 31, 2020,		
	2020	2019	2018
Outstanding stock options	6,262	5,483	4,643
Restricted stock units	1,495	1,127	931
ESPP shares and other	<u>326</u>	<u>19</u>	<u>10</u>
	<u>8,083</u>	<u>6,629</u>	<u>5,584</u>

[Table of Contents](#)**18. Selected quarterly financial data (unaudited)**

The following table contains quarterly financial information for 2020 and 2019. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2020				
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
(in thousands, except per share data)					
Total revenues	\$ 21,863	\$ 198,890	\$ 19,273	\$ 10,708	\$ 250,734
Total operating expenses	225,288	224,835	208,967	214,690	873,780
Loss from operations	(203,425)	(25,945)	(189,694)	(203,982)	(623,046)
Net loss	(202,611)	(21,465)	(194,745)	(199,874)	(618,695)
Net loss per share applicable to common stockholders - basic and diluted	\$ (3.64)	\$ (0.36)	\$ (2.94)	\$ (3.01)	\$ (9.95)
2019					
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
(in thousands, except per share data)					
Total revenues	\$ 12,471	\$ 13,296	\$ 8,910	\$ 9,997	\$ 44,674
Total operating expenses	183,645	215,998	219,326	240,531	859,500
Loss from operations	(171,174)	(202,702)	(210,416)	(230,534)	(814,826)
Net loss	(164,446)	(195,782)	(206,033)	(223,347)	(789,608)
Net loss per share applicable to common stockholders - basic and diluted	\$ (2.99)	\$ (3.55)	\$ (3.73)	\$ (4.04)	\$ (14.31)

**19. Subsequent events**

In January 2021, the Company announced its intent to separate its severe genetic disease and oncology programs into two separate, independent publicly traded companies, bluebird bio, Inc. and a new company, referred to as Oncology NewCo in these consolidated financial statements. bluebird bio, Inc. intends to retain focus on its severe genetic disease programs and Oncology NewCo is expected to focus on the Company's oncology programs. The transaction is expected to be completed in late 2021 and is anticipated to be tax-free, subject to receipt of a favorable IRS ruling.

[Table of Contents](#)**Exhibit Index****Incorporated by Reference**

<b>Exhibit Number</b>	<b>Exhibit Title</b>	<b>Form</b>	<b>File no.</b>	<b>Exhibit</b>	<b>Filing Date</b>
2.1	<a href="#">Stock Purchase Agreement by and between the Registrant and Precision Genome Engineering, Inc.</a>	8-K	001-35966	2.1	June 30, 2014
3.1	<a href="#">Amended and Restated Certificate of Incorporation of the Registrant</a>	8-K	001-35966	3.1	June 24, 2013
3.2	<a href="#">Amended and Restated By-laws of the Registrant</a>	-	-	-	Filed herewith
4.1	<a href="#">Specimen Common Stock Certificate</a>	S-1/A	333-188605	4.1	June 4, 2013
4.2	<a href="#">Description of the Registrant's Securities</a>	-	-	-	Filed herewith
10.1#	<a href="#">Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan, as amended, and forms of award agreement thereunder</a>	S-1	333-188605	10.1	May 14, 2013
10.2#	<a href="#">2010 Stock Option and Grant Plan, as amended, and forms of award agreement thereunder</a>	S-1	333-188605	10.2	May 14, 2013
10.3#	<a href="#">2013 Stock Option and Incentive Plan and forms of award agreement thereunder</a>	S-1/A	333-188605	10.3	June 4, 2013
10.4	<a href="#">Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors</a>	S-1	333-188605	10.4	May 14, 2013
10.5†	<a href="#">Patent License Agreement, dated December 11, 1996, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc., successor-in-interest to Innogene Pharmaceuticals, Inc.) and Massachusetts Institute of Technology, as amended</a>	S-1	333-188605	10.6	May 14, 2013
10.6†	<a href="#">Fourth Amendment to Patent License Agreement, dated October 28, 2016, by and between the Registrant and Massachusetts Institute of Technology</a>	10-K	001-35966	10.7	February 22, 2017
10.7†	<a href="#">Patent and Know-How License Agreement No. 07554F30, dated May 14, 2009, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc.) and INSERM-TRANSFERT, as amended</a>	S-1	333-188605	10.7	May 14, 2013
10.8†	<a href="#">License Agreement, dated September 13, 2011, by and between the Registrant and Institut Pasteur, as amended</a>	S-1	333-188605	10.8	May 14, 2013
10.9†	<a href="#">Amendment No. 3 to License Agreement, dated September 10, 2013, by and between the Registrant and Institut Pasteur</a>	10-Q	001-35966	10.2	November 14, 2013
10.10†	<a href="#">Amendment No. 4 to License Agreement, dated April 1, 2015, by and between the Registrant and Institut Pasteur</a>	10-Q	001-35966	10.1	May 6, 2015
10.11†	<a href="#">License Agreement, dated December 7, 2011, by and between the Registrant and Research Development Foundation</a>	S-1	333-188605	10.9	May 14, 2013
10.12†	<a href="#">Novation Agreement, dated April 2, 2012, by and between the Registrant and The Board of Trustees of the Leland Stanford Junior University</a>	S-1	333-188605	10.1	May 14, 2013
10.13†	<a href="#">Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated March 19, 2013</a>	S-1	333-188605	10.11	May 14, 2013
10.14†	<a href="#">Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated June 3, 2015</a>	10-Q	001-35966	10.14	August 7, 2015
10.15	<a href="#">Amendment No. 1 to Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated February 17, 2016</a>	10-Q	001-35966	10.15	May 4, 2016
10.16	<a href="#">Amendment No. 2 to Amended and Restated Master Collaboration Agreement by and between the Registrant and Celgene Corporation, dated September 28, 2017</a>	10-Q	001-35966	10.17	November 1, 2017
10.17†	<a href="#">Amended and Restated License Agreement by and between the Registrant and Celgene Corporation, dated February 16, 2016</a>	10-Q/A	001-35966	10.16	November 2, 2016

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Exhibit Number	Exhibit Title	Form	Incorporated by Reference		
			File no.	Exhibit	Filing Date
10.18	<a href="#">Second Amended and Restated License Agreement by and between the Registrant and Celgene Corporation and Celgene European Investment Company LLC, dated May 8, 2020</a>	10-Q	001-35966	10.18	August 5, 2020
10.19†	<a href="#">Amended and Restated Co-Development, Co-Promote and Profit Share Agreement by and between the Registrant and Celgene Corporation and Celgene European Investment Company LLC, dated March 26, 2018</a>	10-Q	001-35966	10.20	May 2, 2018
10.20††	<a href="#">First Amendment to Amended and Restated Co-Development, Co-Promote and Profit Share Agreement by and between the Registrant and Celgene Corporation and Celgene European Investment Company LLC, dated May 8, 2020</a>	10-Q	001-35966	10.20	August 5, 2020
10.21†	<a href="#">License Agreement by and between the Registrant and Biogen Idec MA Inc., dated August 13, 2014</a>	10-Q/A	001-35966	10.17	November 2, 2016
10.22†	<a href="#">Letter Agreement by and between the Registrant and Biogen MA Inc., dated September 29, 2017</a>	10-Q	001-35966	10.21	November 1, 2017
10.23†	<a href="#">Exclusive Patent License Agreement by and between the Registrant and the National Institutes of Health, dated August 31, 2015</a>	10-Q/A	001-35966	10.18	November 2, 2016
10.24†	<a href="#">License Agreement, dated December 23, 2015, by and between the Registrant and SIRION Biotech GmbH</a>	10-K	001-35966	10.23	February 21, 2019
10.25††	<a href="#">Toll Manufacturing and Service Agreement, dated November 18, 2016 by and between the Registrant and APCETH Biopharma GmbH, as amended</a>	10-Q	001-35966	10.24	August 1, 2019
10.26††	<a href="#">Clinical and Commercial Supply Agreement - Viral Vector Product, dated November 27, 2017, by and between the Registrant and SAFC Carlsbad, Inc., as amended</a>	10-Q	001-35966	10.25	August 1, 2019
10.27††	<a href="#">Amendment No. 2 to Clinical and Commercial Supply Agreement Viral Vector Product by and between bluebird bio (Switzerland) GmbH and SAFC Carlsbad, Inc.</a>	8-K	001-35966	10.1	January 21, 2020
10.28	<a href="#">Amendment No. 3 to Clinical and Commercial Supply Agreement Viral Vector Product by and between bluebird bio (Switzerland) GmbH and SAFC Carlsbad, Inc.</a>	-	-	-	Filed herewith
10.29#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and Nick Leschly</a>	S-1/A	333-188605	10.12	June 4, 2013
10.30#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and Jeffrey T. Walsh</a>	S-1/A	333-188605	10.13	June 4, 2013
10.31#	<a href="#">Amended and Restated Employment Agreement by and between the Registrant and David M. Davidson, M.D.</a>	S-1/A	333-188605	10.15	June 4, 2013
10.32#	<a href="#">Employment Agreement, dated February 3, 2014, by and between the Registrant and Jason F. Cole</a>	10-Q	001-35966	10.18	May 13, 2014
10.33#	<a href="#">Amendment to Employment Agreement, dated March 7, 2016, by and between the Registrant and Jason F. Cole</a>	10-Q	001-35966	10.25	May 4, 2016
10.34#	<a href="#">Amendment No. 2 to Employment Agreement, dated November 3, 2016, by and between the Registrant and Jason F. Cole</a>	10-K	001-35966	10.27	February 22, 2017
10.35#	<a href="#">Employment Agreement, dated May 30, 2015, by and between the Registrant and Philip D. Gregory</a>	10-Q	001-35966	10.21	August 7, 2015
10.36#	<a href="#">Amendment to Employment Agreement, dated November 3, 2016, by and between the Registrant and Philip D. Gregory</a>	10-K	001-35966	10.31	February 22, 2017
10.37#	<a href="#">2013 Employee Stock Purchase Plan</a>	S-1/A	333-188605	10.17	June 4, 2013
10.38#	<a href="#">First Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan</a>	10-K	001-35966	10.38	February 21, 2018
10.39#	<a href="#">Offer Letter, dated November 16, 2017, by and between the Registrant and Kory Wentworth</a>	10-K	001-35966	10.39	February 21, 2018

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Incorporated by Reference					
Exhibit Number	Exhibit Title	Form	File no.	Exhibit	Filing Date
10.40#	<a href="#">Executive Cash Incentive Bonus Plan</a>	S-1	333-188605	10.18	May 14, 2013
10.41#	<a href="#">Employment Agreement, dated December 18, 2018, by and between the Registrant and William ("Chip") Baird</a>	8-K	001-35966	10.1	February 11, 2019
10.42†	<a href="#">Lease, dated September 21, 2015, by and between the Registrant and ARE-MA Region No. 40 LLC</a>	10-Q	001-35966	10.3	November 5, 2015
10.43	<a href="#">First Amendment to Lease, dated June 21, 2016, by and between the Registrant and ARE-MA Region No. 40 LLC</a>	10-Q	001-35966	10.37	August 3, 2016
10.44	<a href="#">Second Amendment to Lease, dated November 14, 2016, by and between the Registrant and ARE-MA Region No. 40 LLC</a>	10-K	001-35966	10.44	February 22, 2017
10.45††	<a href="#">Sublease, dated April 16, 2019, by and between the Registrant and Aventis Inc.</a>	10-Q	001-35966	10.42	August 1, 2019
10.46	<a href="#">Amendment to Sublease, dated April 19, 2019, by and between the Registrant and Aventis Inc.</a>	10-Q	001-35966	10.43	August 1, 2019
21.1	<a href="#">Subsidiaries of the Registrant</a>	-	-	-	Filed herewith
23.1	<a href="#">Consent of Ernst &amp; Young LLP</a>	-	-	-	Filed herewith
31.1	<a href="#">Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</a>	-	-	-	Filed herewith
31.2	<a href="#">Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</a>	-	-	-	Filed herewith
32.1	<a href="#">Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.</a>	-	-	-	Furnished herewith
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document)				
101.SCH	Inline XBRL Taxonomy Extension Schema Document.	-	-	-	Filed herewith
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.	-	-	-	Filed herewith
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.	-	-	-	Filed herewith
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.	-	-	-	Filed herewith
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.	-	-	-	Filed herewith
104	Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101)	-	-	-	Filed herewith

† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been submitted separately to the SEC.

†† Portions of this exhibit (indicated by asterisks) have been omitted in accordance with the rules of the SEC.

# Indicates a management contract or any compensatory plan, contract or arrangement.

[Table of Contents](#)**SIGNATURES**

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

**bluebird bio, Inc.**By: /s/ Nick Leschly

Nick Leschly

President, Chief Executive Officer and Director

**SIGNATURES AND POWER OF ATTORNEY**

We, the undersigned directors and officers of bluebird bio, Inc. (the “Company”), hereby severally constitute and appoint Nick Leschly and Chip Baird, and each of them singly, our true and lawful attorneys, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this Power of Attorney.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ Nick Leschly Nick Leschly	President, Chief Executive Officer and Director <i>(Principal Executive Officer and Duly Authorized Officer)</i>	February 23, 2021
/s/ Chip Baird Chip Baird	Chief Financial Officer <i>(Principal Financial Officer, Principal Accounting Officer, and Duly Authorized Officer)</i>	February 23, 2021
/s/ Daniel S. Lynch Daniel S. Lynch	Director	February 23, 2021
/s/ John O. Agwunobi, M.D. John O. Agwunobi, M.D.	Director	February 23, 2021
/s/ Wendy L. Dixon, Ph.D. Wendy L. Dixon, Ph.D.	Director	February 23, 2021
/s/ Ramy Ibrahim, M.D. Ramy Ibrahim, M.D.	Director	February 23, 2021
/s/ William R. Sellers, M.D. William R. Sellers, M.D.	Director	February 23, 2021
/s/ Denice Torres Denice Torres	Director	February 23, 2021
/s/ Mark Vachon Mark Vachon	Director	February 23, 2021

# EXHIBIT K



Document title: collaborations

Capture URL: <https://www.bluebirdbio.com/about-us/collaborations>

Page loaded at (UTC): Wed, 20 Oct 2021 14:44:04 GMT

Capture timestamp (UTC): Wed, 20 Oct 2021 14:44:31 GMT

Capture tool: v7.12.2

Collection server IP: 54.157.181.49

Browser engine: Chrome/77.0.3865.120

Operating system: Microsoft Windows NT 10.0.17763.0 (10.0.17763.0)

PDF length: 6

Capture ID: cbe90a69-d903-45e6-ac15-811d4b872723

User: loeb-jgorruso

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## collaborations

### our partnering strategy

We are developing therapies that have the potential to transform the lives of people with severe genetic and rare diseases and cancer. Our current platform is just the beginning. We are committed to continuing to develop gene therapy technologies and capabilities that have broad potential beyond the core indications.

We are actively seeking collaborators and licensing opportunities in the U.S. and around the world to explore the therapeutic potential of our technologies in new cell types and diseases.

### what we're looking for

We are actively seeking collaborators, in- and out-licensing opportunities to fully leverage the transformational therapeutic potential of our platforms. Specific areas of interest include:

- Novel and impactful applications of bluebird's megaTAL gene editing technology
- CAR T / TCR immunotherapy targets with highly tumor-specific expression profiles
- Clinically-relevant CAR T / TCR immunotherapy programs with

- Novel and impactful applications of bluebird's megaTAL gene editing technology
- CAR T / TCR immunotherapy targets with highly tumor-specific expression profiles
- Clinically-relevant CAR T / TCR immunotherapy programs with compelling and comprehensive preclinical POC data
- Novel technologies which may enhance key features of CAR T / TCR immunotherapies
- Clinically-relevant viral vector-based gene therapy programs for severe genetic diseases with compelling and comprehensive preclinical POC data
- Novel technologies which may enhance key features of hematopoietic stem cell-based lentiviral gene therapy

## contact us

Are you interested in partnering with bluebird? Please contact us at  
[partner@bluebirdbio.com](mailto:partner@bluebirdbio.com)

## our current partners



bluebird bio and Bristol Meyers Squibb (BMS) are collaborating to develop CAR T cell therapies targeting BCMA. The collaboration's lead oncology program, bb2121, is currently being studied for the treatment of relapsed and refractory multiple myeloma. For bb2121, bluebird and BMS have joint responsibility for development, manufacturing and commercialization in the United States. BMS will assume sole responsibility for drug product manufacturing and commercialization outside the United States. bluebird bio and BMS are also working together on a second clinical-stage anti-BCMA CAR T program, bb2121.



In November 2019, we entered into a research collaboration to pursue clinical proof-of-concept for Forty Seven's novel antibody-based conditioning regimen, FSI-174 (anti-cKIT antibody) plus magrolimab (anti-CD47 antibody), with bluebird's ex vivo lentiviral vector hematopoietic stem cell (LVV HSC) gene therapy platform. This collaboration will focus on a conditioning approach aimed to deliver reduced toxicity and will initially target diseases that have the potential to be corrected with transplantation of autologous gene-modified blood-forming stem cells. If successful, the new conditioning regimen could allow for more patients to undergo gene therapy.





In August 2018, we entered into a strategic research and development collaboration with Gritstone Oncology to identify tumor-specific targets and natural T-cell receptors (TCRs) directed to those targets for use in our established cell therapy platforms.

Under the agreement, Gritstone Oncology will provide 10 tumor-specific targets across several tumor types and, in certain cases, TCRs directed to our targeted indications and will utilize its proprietary technology platform to enable patient selection for clinical development of such therapies.



In January 2019, we announced we have entered into an exclusive license agreement to research, develop and commercialize chimeric antigen receptor (CAR) T cell therapies using Inhibrx's proprietary single domain antibody (sdAb) platform to multiple cancer targets. The small size of sdAbs may enable the generation of more complex CAR T cell products such as those designed to combine additional functions into a single CAR molecule or recognize multiple tumor antigens simultaneously.

Under the terms of the license agreement, Inhibrx will provide bluebird bio the exclusive worldwide rights to develop, manufacture and commercialize certain cell therapy products containing sdAbs directed to various cancer targets. bluebird bio will be responsible for the clinical development and commercialization of the cancer-targeting CAR-T products.



In June 2016, we entered into a strategic manufacturing agreement with Lonza Houston, Inc., providing for the future commercial production of our drug products: ZYNTEGLO™ for transfusion-dependent β-thalassemia and Lenti-D™ in cerebral adrenoleukodystrophy.

This agreement follows a successful multi-year clinical manufacturing relationship and provides us with a path to commercial supply including dedicated production suites within Lonza's state-of-the-art facility. Under this multi-year agreement, Lonza will complete the suite design, construction and validation along with process validation prior to anticipated commercial launch.



In September 2016, we entered into a strategic research and development collaboration and licensing agreement with Medigene AG for T cell receptor (TCR) immunotherapies against four targets. In this partnership, Medigene will be responsible for the generation and delivery of the TCRs using its TCR isolation and characterization platform. Following the collaborative preclinical development, bluebird bio will assume sole responsibility for the clinical development and commercialization of the TCR product candidates and will receive an exclusive license for the intellectual property covering the resulting TCRs.



Following the collaborative preclinical development, bluebird bio will assume sole responsibility for the clinical development and commercialization of the TCR product candidates and will receive an exclusive license for the intellectual property covering the resulting TCRs.



In December 2016, we entered into a strategic manufacturing partnership with Minaris Regenerative Medicine GmbH ("Minaris") for the future European commercial production of ZYNTEGLO™ for transfusion-dependent β-thalassemia (TDT) and our Lenti-D™ product candidate for cerebral adrenoleukodystrophy (CALD). Under this multi-year agreement, Minaris performs clinical manufacturing, process validation activities and commercial manufacturing for ZYNTEGLO and Lenti-D drug product to support the treatment of patients with TDT and CALD, respectively.

In May 2020, we expanded our manufacturing partnership agreement with Minaris to include late stage and commercial drug product manufacturing in both the United States and Europe for LentiGlobin™ for the treatment of patients with sickle cell disease (SCD). This partnership expansion follows a successful multi-year manufacturing relationship and provides us with commercial manufacturing capabilities in both Europe and U.S., including dedicated production suites within Minaris' state-of-the-art facilities.



In October of 2019, we entered into a research collaboration to jointly develop next-generation in vivo genome editing treatments for genetic diseases, including hemophilia. During the three-year research collaboration, we'll will focus on identifying a development gene therapy candidate with the ambition of offering people with hemophilia A a lifetime free of factor replacement therapy.

The research collaboration will utilize bluebird bio's proprietary mRNA-based megaTAL™ technology that has the potential to provide a highly specific and efficient way to silence, edit or insert genetic components. Aligned with Novo Nordisk's haemophilia portfolio, the research collaboration will initially focus on correcting FVIII-clotting factor deficiency, with the potential to explore additional therapeutic targets.

## REGENERON

In August 2018, we announced a tactical collaboration with Regeneron to apply our respective technology platforms to the discovery, development and commercialization of novel immune cell therapies for cancer.

Under the agreement, we will each leverage Regeneron's VelociSuite® platform technologies for the discovery and characterization of fully human antibodies, as well as T-cell receptors directed against tumor-specific proteins and peptides. In addition, we have jointly selected six initial targets and will equally share the costs of research and development up to the point of submitting an IND application. Under this five-year agreement, additional targets may be selected. When an IND is submitted for a potential cell therapy product, Regeneron will have the right to opt-in to a co-development/co-commercialization arrangement for certain collaboration targets.





In October of 2019, we entered into a research collaboration to jointly develop next-generation in vivo genome editing treatments for genetic diseases, including hemophilia. During the three-year research collaboration, we'll will focus on identifying a development gene therapy candidate with the ambition of offering people with hemophilia A a lifetime free of factor replacement therapy.

The research collaboration will utilize bluebird bio's proprietary mRNA-based megaTAL™ technology that has the potential to provide a highly specific and efficient way to silence, edit or insert genetic components. Aligned with Novo Nordisk's haemophilia portfolio, the research collaboration will initially focus on correcting FVIII-clotting factor deficiency, with the potential to explore additional therapeutic targets.

## REGENERON

In August 2018, we announced a tactical collaboration with Regeneron to apply our respective technology platforms to the discovery, development and commercialization of novel immune cell therapies for cancer.

Under the agreement, we will each leverage Regeneron's VeloSuite® platform technologies for the discovery and characterization of fully human antibodies, as well as T-cell receptors directed against tumor-specific proteins and peptides. In addition, we have jointly selected six initial targets and will equally share the costs of research and development up to the point of submitting an IND application. Under this five-year agreement, additional targets may be selected. When an IND is submitted for a potential cell therapy product, Regeneron will have the right to opt-in to a co-development/co-commercialization arrangement for certain collaboration targets.



In December 2017, we entered into a strategic research collaboration and licensing agreement with TC BioPharm to discover and develop gamma delta CAR T cell product candidates for cancer immunotherapy.

Under the terms of the agreement, TC BioPharm is responsible for development of all targets through Phase 1/2, at which point we have the exclusive option to assume sole responsibility for further clinical development and commercialization on a global basis.



### QUICK LINKS

- [PATIENTS & ADVOCACY](#)
- [INVESTORS & MEDIA](#)
- [CAREERS](#)
- [CONTACT US](#)

### CONTACT INFO

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- [INVESTOR@BLUEBIRDBIO.COM](mailto:INVESTOR@BLUEBIRDBIO.COM)
- [MEDINFO@BLUEBIRDBIO.COM](mailto:MEDINFO@BLUEBIRDBIO.COM)



# EXHIBIT L

## EXHIBIT L

U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
1.0	A recombinant vector comprising	<p>The following vector is a “recombinant vector”: BB305 vector.</p> <p><u>Exemplary support:</u></p> <p>U.S. Patent No. 7,541,179 (“the ’179 Patent”) defines “recombinant lentiviral vector” as follows:</p> <p>“The term ‘recombinant lentiviral vector’ refers to an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation.” ’179 Patent, at Col. 2: 36-40.</p> <p>The publication by Negre et al., 2015, <i>Preclinical Evaluation of Efficacy and Safety of an Improved Lentiviral Vector for the Treatment of β-Thalassemia and Sickle Cell Disease</i>, <i>Current Gene Therapy</i>, Vol. 15, pp. 64-81 (hereafter, “Negre 2015”), describes the derivation of the BB305 vector from the lentiviral vector HPV569:</p> <p>“A previously published clinical trial demonstrated the benefit of autologous CD34<sup>+</sup> cells transduced with <i>a self-inactivating lentiviral vector (HPV569) containing an engineered β-globin gene (β<sup>A-T87Q</sup>-globin)</i> in a subject with β-thalassemia major. <i>This vector has been modified to increase transduction efficacy without compromising safety. . . This comprehensive efficacy and safety data provided the basis for initiating two clinical trials with this second generation vector (BB305) in Europe and in the USA in patients with β-thalassemia major and sickle cell disease.</i></p> <p>...</p> <p><b>LentiGlobin BB305 Lentiviral Vector Titer and In vitro Transduction Efficiency</b></p> <p>We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the β<sup>A-T87Q</sup>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both</p>

**EXHIBIT L**

U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p><i>lentiviral vectors[,] and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remained unchanged.</i>” Negre 2015, at 64 (abstract) and 68 (emphasis and italics added).</p>
1.1	a nucleic acid encoding a functional globin operably linked to	<p>The following recombinant vector comprises “a nucleic acid encoding a functional globin”: BB305 vector.</p> <p><u>Exemplary support:</u></p> <p>“The term ‘functional globin gene’ refers to a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene.” ’179 Patent, at col. 2:41-45.</p> <p>“The functional globin gene may encode a wild-type globin appropriate for a mammalian individual to be treated, or it may be a mutant form of globin, preferably one which provides for superior properties, for example superior oxygen transport properties. <i>The functional globin gene includes both exons and introns, as well as globin promoters and splice donors/acceptors.</i> Suitably, the globin gene may encode α-globin, β-globin, or γ-globin. β-globin promoters may be sued [sic] with each of the globin genes.” <i>Id.</i> at col. 2:45-53 (italics and emphasis added).</p> <p>As shown in Figure 1A of Negre 2015 (reproduced on the following page), the BB305 vector encodes a functional globin, as it contains within it β-globin exons 1 to 3, β-globin introns 1 and 2, a β-globin promoter and enhancer, and DNase I hypersensitivity sites 2, 3 and 4 (HS2, HS3, and HS4). All of these features have been highlighted in yellow in Figure 1A:</p>

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p><b>A</b></p>
1.2	a 3.2-kb nucleotide fragment which consists essentially of three contiguous	<p>“<b>Fig. (1).</b> <i>In vitro</i> evaluation of LentiGlobin lentiviral vectors. <b>A) Diagram of the LentiGlobin HPV569 and BB305 lentiviral vectors.</b> The 3' <math>\beta</math>-globin enhancer, the 372 base pairs (bp) IVS2 deletion in intron 2 (triangle), the <math>\beta^{A-T87Q}</math> mutation (ACA [Thr] to CAG [Gln]) and DNase I hypersensitive sites (HS) 2, HS3, and HS4 of the human <math>\beta</math>-globin locus control region (LCR) are indicated. Safety modifications including the 400 bp deletion in the U3 of the right HIV LTR, the rabbit <math>\beta</math>-globin polyA signal and the 2 x 250 bp cHS4 chromatin insulators are indicated. <math>\beta</math>p, human <math>\beta</math>-globin promoter; cPPT/flap, central polypurine tract; HIV LTR, human immunodeficiency type-1 virus long-terminal repeat; ppt, polypurine tract; RRE, Rev-responsive element; <math>\Psi^+</math>, packaging signal. . . .”</p> <p>Negre 2015, at 66 (Figure 1 and legend) (italics and emphasis added).</p> <p>A Person of Ordinary Skill in the Art (“POSA”), reviewing the Negre 2015 publication in light of general knowledge, would understand that the BB305 vector contains a nucleic acid encoding a functional human <math>\beta</math>-globin gene.</p> <p>The BB305 vector meets the claim limitation of “a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human <math>\beta</math>-globin locus control region (LCR)”.</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
nucleotide fragments obtainable from a human β-globin locus control region (LCR),	<p><u>Exemplary support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way (to obtain the same result) as the vectors claimed in the ’179 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>A POSA would read the information in May et al., <i>Therapeutic haemoglobin synthesis in β-thalassemic mice expressing lentivirus-encoded human β-globin</i>, <i>Nature</i>, Vol 406, pp. 82-86 (July 6, 2000) (hereafter “May 2000”) and the prosecution history for US Patent Application No. 10/188221 (hereafter “the ’221 Application”), and understand them as indicating that the new vectors described therein (and claimed in the ’179 Patent) occupied a middle ground between the prior art vectors that contained minimal LCRs and the prior art vectors that contained much larger LCRs. For example, May 2000 states:</p> <p style="padding-left: 2em;">“Incorporation of small elements spanning DNase HS2, HS3 and HS4 into viral vectors increases β-globin expression in mouse erythroleukaemia (MEL) cells<sup>9,10</sup>. However, low-level expression, strong position effects and transcriptional inactivation are still observed in bone marrow chimaeras<sup>5,11</sup>. Studies in transgenic mice<sup>12</sup> and deletional analyses<sup>13</sup> support the view that coordinated interaction of several genetic elements including the LCR is required for physiologic β-globin gene expression<sup>12-15</sup>. We therefore thought that incorporation of large elements spanning HS2, HS3 and HS4<sup>16-18</sup> in a vector might enhance β-globin expression beyond levels previously achieved using arrayed minimal core elements<sup>5,9-11</sup>, and thus might diminish position effects and vector silencing. The efficient transduction of large genomic fragments using onco-retroviral vectors has proved to be severely curtailed by splicing and other alterations affecting the stability of the recombinant genomes<sup>9,10,16</sup>. Here we report how these problems may be overcome by using vectors derived from human immunodeficiency virus 1, a retrovirus that has the ability to regulate packaging of unspliced viral genomes. We constructed two recombinant lentiviruses carrying β-globin transcription units (Fig. 1a, b). RNS1 contains a minimal LCR comprising previously tested core elements of HS2, HS3 and HS4 (ref. 9).” May 2000, at p. 82 (italics and emphasis added).</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>This contention is supported by multiple statements in the prosecution history of the patent application that ultimately issued as the '179 Patent (the '221 Application). For example, the Applicants for the '221 Application stated:</p> <p style="padding-left: 40px;">“The nature of the invention identifies the field of the endeavor—here a recombinant vector for treating hemoglobinopathies by expressing a functional globin <i>in vivo</i> using the claimed 3.2-kb portion of a human β-globin LCR. As an aside, . . . the Examiner characterized the three fragments in the LCR as ‘essential elements from the β-globin LCR.’ Applicants wish to clarify this remark as it is not a term of art and is somewhat misleading. <i>The literature describes core HS sites as small fragments, and these core sequences might be considered as ‘essential’ or ‘minimal’ since they are the smallest fragments that can effect globin expression. In point of fact, the present invention resides in having more than these small core sequences, namely, the invention resides in having the larger, specific HS-containing fragments in the vector and obtaining a level of globin expression not previously possible in vivo.</i>”</p> <p style="padding-left: 40px;">09/12/2007 Rule 116 Amendment and Response for the '221 Application, at p. 13 (hereafter “09/12/2007 Response”) (italics and emphasis added).</p> <p>In fact, Applicants specifically pointed out to the United States Patent &amp; Trademark Office (“USPTO”) Examiner that prior art vectors had human β-globin LCR fragments that ranged in size from very large (20 kb) to very small (1 kb):</p> <p style="padding-left: 40px;">“As mentioned, the human β-globin LCR is a 20-30 kb region extending upstream from the start of the ε-globin gene. The region has been extensively analyzed and the scientific literature reports a variety of expression studies with a 20-kb ‘minilocus,’ a 6.5-kb [‘microlocus’] and a 1-kb fragment with core DNase I hypersensitive site[s].”</p> <p style="padding-left: 40px;">09/12/2007 Response, at p. 10 (internal citations omitted).</p> <p>The Applicants distinguished their claims from the prior art by contending that, to their knowledge, “no previous studies have been conducted with a 3.2-kb portion of a human β-globin LCR as claimed herein.” <i>Id.</i></p> <p>Because the descriptions of the core sequences for the HS2, HS3 and HS4 regions were known in the prior art, the Applicants asserted that not only should one assume the DNase hypersensitivity-</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>spanning fragments “<i>are at least as big as their corresponding core sequences</i>”, but also that a POSA would “<i>know[], in fact, that they must be larger.</i>” 09/12/2007 Declaration of Jason W. Plotkin Under 37 C.F.R. §1.132 (hereafter, “Plotkin Declaration”) at ¶ 36 (italics added), as submitted with 09/12/2007 Response.</p> <p>In particular, a POSA would know that incorporation of only the “core” LCR fragments resulted in vectors with low viral titers that were “highly unstable with multiple rearrangements of the transferred proviral structures.” See Negre <i>et al.</i>, 2016, <i>Gene Therapy of the β-Hemoglobinopathies by Lentiviral Transfer of the βA(T87Q)-Globin Gene, Human Gene Therapy</i>, Vol. 27, No. 2: 148- 165, at p. 154 (hereafter, “Negre 2016”) (internal citations omitted). In addition, a POSA would have been aware that “[r]educing the size of the LCR to minimal elements is unsatisfactory as β-globin expression levels are too low.” <i>Id.</i> (citing references from 1992-1997); <i>see also</i>, May 2000, at p. 82. Accordingly, a POSA would understand that the claimed vectors needed to have an HS2-HS3-HS4 LCR region that was bigger than 1 kb (<i>i.e.</i>, had more than the minimal core HS sequences).</p> <p>In addition to setting a lower 1 kb boundary, the Applicants for the ’221 Application provided a flexible upper boundary of approximately 3.2 kb for the combined HS-spanning nucleotide fragments when they argued to the USPTO that:</p> <p>“The simple fact that the combination of the three HS-spanning fragments is 3.2 kb partially (and significantly) closes this aspect of the present claim, <i>qualifies its size and thus provides the boundaries for ascertaining the elements excluded by use of ‘consisting essentially of’ as the transitional phrase.</i> For example, any additional nucleotides added to the 3.2 kb fragment that cause the fragment to exceed 3.2 kb, would alter a basic and novel property of the invention. As <i>Applicants have exhaustively established on the record, the combined size of the three HS-spanning fragments so closely approximates 3.2 kb, that the number of additional nucleotides that could be added to (or removed from) this fragment is relatively few and non-material. For example, the types of non-material nucleotide changes that can be accommodated are . . . adding a small linker to provide or change a restriction site, or making any other minor change to the sequence that does not alter the functionality of the fragment in driving globin expression, including changes at the ends of or at the junction points of the fragments.</i> All such changes are well known in the art and would be readily contemplated, accomplished and analyzed by skilled artisans. <i>However, none of these non-material changes rises to the level of the fragments</i></p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>taught by Ryan or Antoniu. . . . Ryan shows only a 30-kb and a 22-kb recombinant nucleotide fragment that contain at least HS2, HS3, and HS4. . . . . Antoniu show[s] only a single 5.5 kb nucleotide fragment that contains HS2, HS3 and HS4. Based on size, the Ryan and Antoniu fragments clearly differ from the 3.2 kb fragment of Claim 1.</i></p> <p>Further, based on nucleotide composition and arrangement of the HS fragments (i.e., which pieces of the LCR are present), <i>neither Ryan nor Antoniu shows any fragment that combines the recited HS2-, HS3- and HS4-spanning fragments in contiguity into a single 3.2-kb fragment as claimed in present Claim 1.</i> Ryan’s fragments are single, large restriction fragments from the LCR encompassing all 5 HS sites in their natural order and sequence context. Antoniu fragments combine various restriction fragments which are larger and distinct from those claimed by Applicants. Merely because the three HS fragments that Applicants have identified are within the sequence of the Ryan and Antoniu fragments does not mean that those references “encompass” the claimed 3.2-kb fragment and thereby anticipate the present invention. <i>The actual combination must be demonstrated in these references and it is not, as evidenced by Applicants’ use of ‘consisting essentially of’ as the transitional phrase, along with bounding this operable LCR fragment at 3.2 kb, which, therefore, serve to distinguish the claimed invention from Ryan and Antoniu as well as establish the basic and novel properties of this nucleotide fragment.”</i></p> <p>12/03/2008 Amendment and Response After Final Office Action for the ’221 Application, at pp. 9-10 (italics and emphasis added).</p> <p>Thus, a POSA would understand, based on these comments in the prosecution history for the ’221 Application, that the claimed vectors in the ’179 Patent encompass vectors with LCR regions that differ in size and in sequence identity from the 3.2 kb human β-globin LCR fragment identified in the Plotkin Declaration, provided that these differences do not bring the LCR fragment to a size that is much greater than 3.2 kb, or materially alter its function.</p> <p>“As apparent from the reference sequence, and as known in the art, <i>the three fragments that form the 3.2-kb portion of the LCR are assembled from non-contiguous portions of the LCR.</i> In this regard, it should be recognized that these fragments can be joined in either 5’-3’ or 3’-5’ orientation using any of numerous techniques known to those of skill in the art to provide further vector examples. <i>Once assembled into a vector, the fragments need not be cleavable nor must the entire restriction recognition site be present.</i> For example, one skilled in the art will readily</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>[sic] appreciate that the full restriction site might not be present if the fragment is blunt-ended before ligation, yet it may be present if the cut site is filled before ligation.”</p> <p>09/12/2007 Response, at p. 15 (italics and emphasis added).</p> <p>A POSA would also readily understand that the sequence for a human gene, particularly a gene such as human <math>\beta</math>-globin, will change over time as sequencing techniques and technologies improve. The Applicants for the ’221 Application admitted that the “globin genes were among the first ever sequenced at the nucleotide level.” 9/12/2007 Response, at p. 7. The Applicants also admitted in 2007 that “When accessing NG_000007 at present, one obtains version 3, which in relevant part includes an additional approximately 9kb upstream of the version 1. <i>Hence the numbering of the nucleotides is offset between the versions, and can be further slightly offset by polymorphisms and minor variations.</i>” <i>Id.</i> (italics and emphasis added). This, combined with the fact that the claims of the ’179 Patent refer to “a” human <math>\beta</math>-globin LCR rather than “the” human <math>\beta</math>-globin LCR, would indicate to a POSA that it is the size of the HS-spanning fragments that is most important, and sequence variation in the HS-spanning LCR fragment of the claimed vectors is permitted, provided that it does not substantially alter the vector’s properties.</p> <p>Figure 1A of Negre 2015 is reproduced in part below with its globin-related elements highlighted in yellow.</p> <p><b>Fig. (1).</b> <i>In vitro evaluation of LentiGlobin lentiviral vectors. A) Diagram of the LentiGlobin HPV569 and BB305 lentiviral vectors. The 3' <math>\beta</math>-globin enhancer, the 372 base pairs (bp) IVS2 deletion in intron 2 (triangle), the <math>\beta^{\text{A-T87Q}}</math> mutation (ACA [Thr] to CAG [Gln]) and DNase I hypersensitive sites (HS) 2, HS3, and HS4 of the human <math>\beta</math>-globin locus control region (LCR) are indicated. Safety modifications including the 400 bp deletion in the U3 of the right HIV LTR, the rabbit <math>\beta</math>-globin polyA signal and the 2 x 250 bp cHS4 chromatin insulators are indicated. <math>\beta</math>p, human <math>\beta</math>-globin promoter; cPPT/flap, central polypurine tract;</i></p>

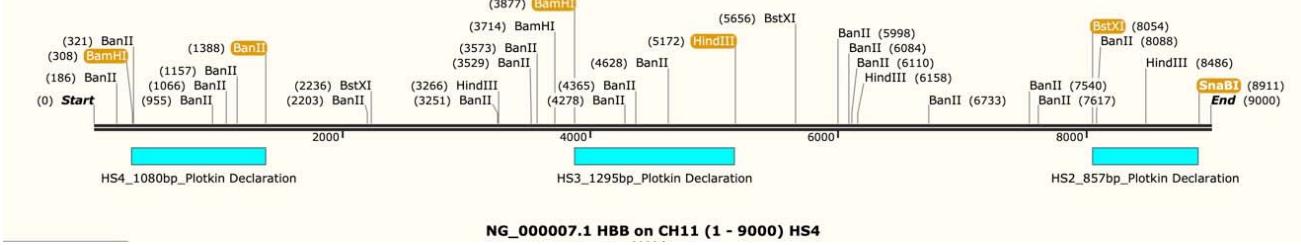
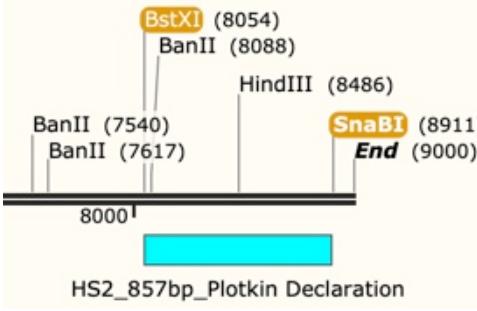
**EXHIBIT L**

U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>HIV LTR, human immunodeficiency type-1 virus long-terminal repeat; ppt, polypurine tract; RRE, Rev-responsive element; <math>\Psi^+</math>, packaging signal. . . .”</p> <p>Negre 2015, at 66 (Figure 1 and legend) (italics and emphasis added).</p> <p>Based on Figure 1A of Negre 2015, as well as their general knowledge, a POSA would readily understand that the BB305 vector encodes a mutated (T87Q) human <math>\beta</math>-globin gene operably linked to a 2.7 kb human <math>\beta</math>-globin LCR region.</p> <p>A POSA would further understand that the BB305 vector, with its 2.7 kb human <math>\beta</math>-globin LCR region, performs the same function as the vectors claimed in the ’179 Patent (enhancing <math>\beta</math>-globin expression beyond levels previously achieved) in the same way: through the incorporation of fragments of the HS2, HS3, and HS4 DNase I hypersensitive sites obtained from a human <math>\beta</math>-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>A POSA would also know that the BB305 vector achieves the same result as the vectors claimed in the ’179 Patent – the correction of hemoglobinopathies in animal or human cells. For example, the Negre 2015 publication states that the BB305 vector was able to correct a <math>\beta</math>-thalassemic phenotype in mice:</p> <p style="padding-left: 40px;"><i>“In conclusion, overall phenotype correction of <math>\beta</math>-thalassemic mice was observed with both LentiGlobin HPV569 and BB305 lentiviral vectors with no alteration of bone marrow homeostasis in the primary transplant animals. . . . Clinical trials of BB305 are underway in both <math>\beta</math>-thalassemia and sickle cell disease in Europe and for <math>\beta</math>-thalassemia in the USA. Preliminary clinical results showing the advantage of the new Lentiglobin BB305 lentiviral vector over the previous HPV569 vector in <math>\beta</math>-thalassemia patients were reported at the 2014 annual meeting of the European Hematology Association and the 2014 annual meeting of the American Society of Hematology . . . .”</i></p> <p>Negre 2015, p. 78 (italics and emphasis added).</p>

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
1.3	the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the claim limitation of “the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the ’179 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the ’221 Application that matured into the ’179 Patent, the claimed vector “comprises a 3.2-kb portion <b>of a human β-globin locus control region (LCR) consisting essentially of 3 restriction fragments</b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the ’221 Application. This declaration used the human β-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). <i>See Plotkin Declaration, ¶¶ 18 and 29.</i></p> <p>A POSA can take this same β-globin sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human β-globin LCR region. <i>See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</i></p>

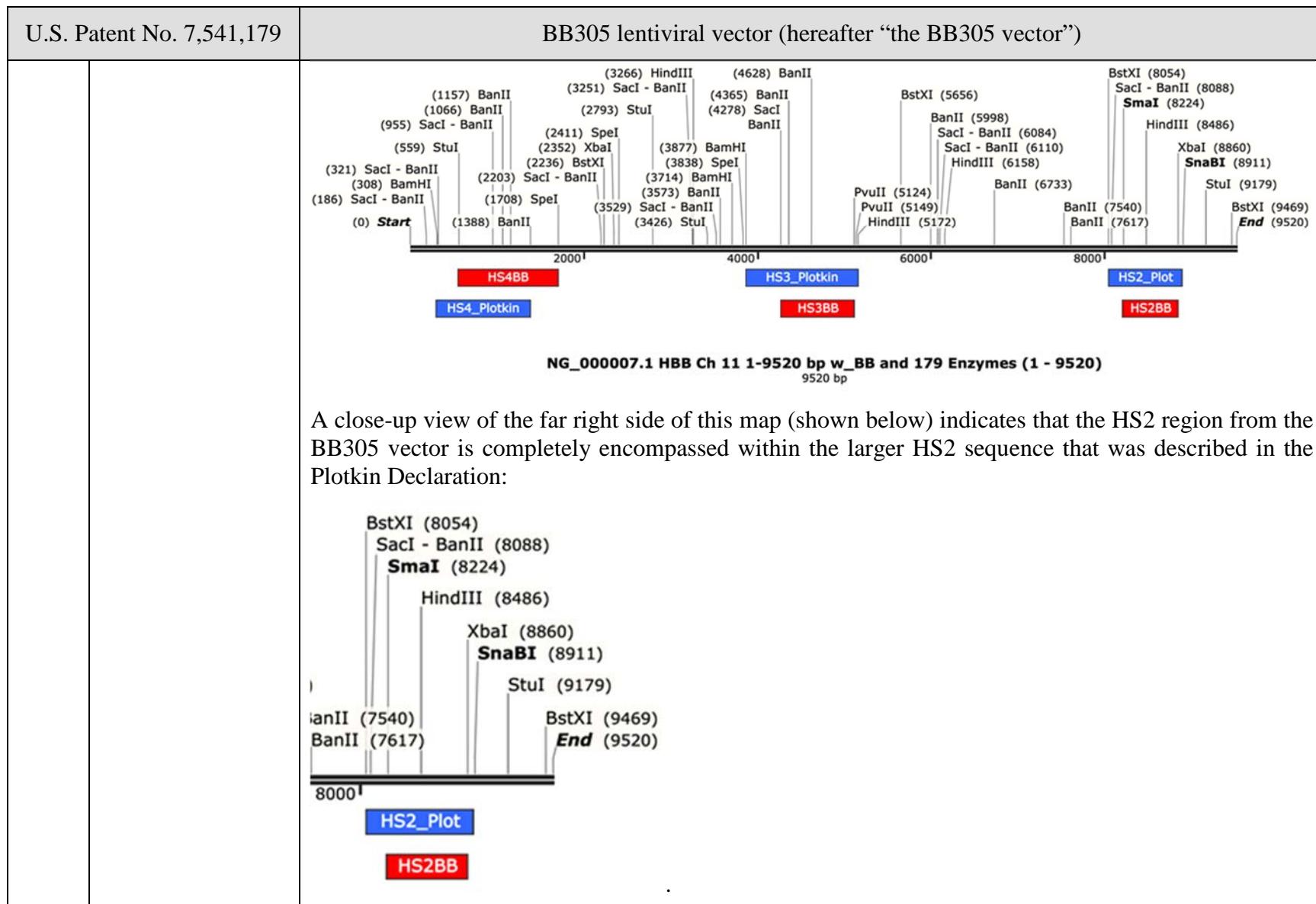
## EXHIBIT L

U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p data-bbox="206 200 1909 257">BB305 lentiviral vector (hereafter “the BB305 vector”)</p>  <p data-bbox="587 567 1888 592">NG_000007.1 HBB on CH11 (1 - 9000) HS4</p> <p data-bbox="587 576 1888 869">The double black line in this HS fragment map above represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '179 Patent are shown: (SnaBI, BstXI, HindIII, BamHI and Ban II). Note that although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, <b>only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange</b>. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.</p> <p data-bbox="587 886 1888 959">A close-up view of this HS fragment map, which focuses on the far right region encompassing the HS2 fragment, is provided below:</p>  <p data-bbox="587 1310 1888 1416">The HS2 segment, represented by the blue box, is 857 base pairs in length. It is bordered by the SnaBI restriction enzyme recognition site on the right, and the BstXI restriction enzyme recognition site on the left.</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>Based on this analysis and other publicly available information, a POSA would understand that the HS2 fragment in the HPV569 and BB305 vector, although identified using different restriction enzymes, is nonetheless highly similar to and performing the same function as the HS2 fragment recited in the '179 Patent claims.</p> <p>For example, a POSA would understand based on publicly available information and general knowledge that HS2 fragment within the HPV569 vector is approximately 644 bp in length and located between SmaI and XbaI restriction enzyme sites. In addition, a POSA would also know that the sequences of the HPV569 and BB305 vector are identical in the 2.7 kb β-globin LCR region. <i>See, e.g., Negre 2015, at 68 (“We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of the 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta^{A-T87Q}</math>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p> <p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS2 sequence for the BB305 vector onto the same human β-globin LCR region described in the Plotkin Declaration. Below is such a map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS2 fragment from the BB305 vector is on the far right-hand side image.</p>

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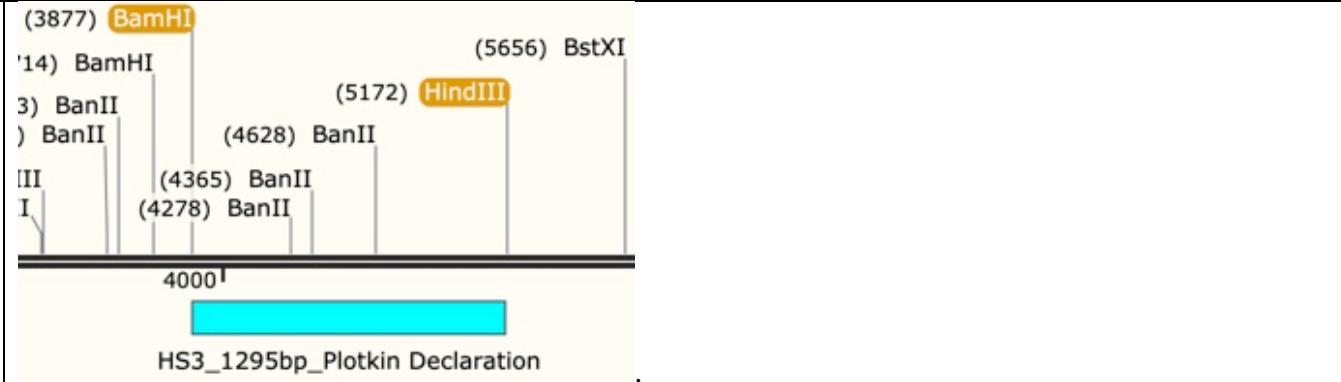
**EXHIBIT L**

U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS2 fragment within the BB305 vector is highly similar to the HS2 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the HS2 sequence within the BB305 vector is equivalent to a “SnaBI and BstXI HS2-spanning nucleotide fragment of said LCR”, (e.g., the HS2 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector.</p>
1.4	a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR	<p>The BB305 vector meets the claim limitation of “a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the ’179 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the ’221 Application that matured into the ’179 Patent, the claimed vector “comprises a 3.2-kb portion <b>of a human β-globin locus control region (LCR) consisting essentially of 3 restriction fragments</b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the ’221</p>

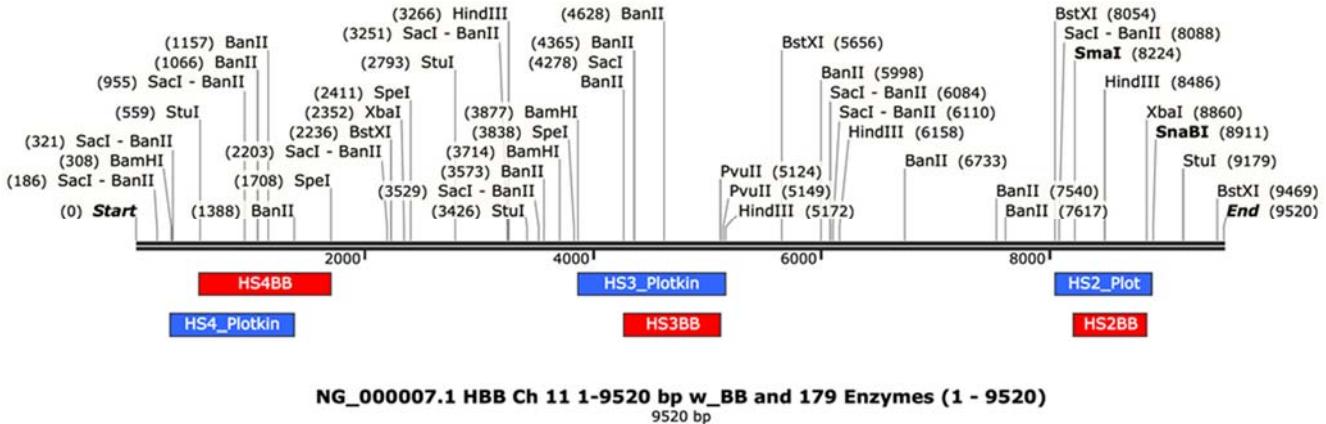
## EXHIBIT L

U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>Application. This declaration used the human <math>\beta</math>-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). See Plotkin Declaration, ¶¶ 18 and 29.</p> <p>A POSA can take this same <math>\beta</math>-globin sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human <math>\beta</math>-globin LCR region. See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</p> <p>The double black line in this HS fragment map above represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the ’179 Patent are shown: (SnaBI, BstXI, HindIII, BamHI and Ban II). Note that although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, <b>only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange</b>. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.</p> <p>A close-up view of this HS fragment map, which focuses on the middle region encompassing the HS3 fragment, is provided below:</p>

## EXHIBIT L

U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	 <p>The diagram illustrates the BB305 lentiviral vector structure. It features a horizontal black bar representing the vector backbone. Several vertical grey lines indicate restriction enzyme cleavage sites: '14) BamHI' at position 3877, '3) BanII' at 4142, ') BanII' at 4142, 'III' at 4142, 'I' at 4142, '(4365) BanII' at 4278, '(4278) BanII' at 4278, '(4628) BanII' at 4628, '(5172) HindIII' at 5172, and '(5656) BstXI' at 5656. A blue horizontal bar labeled 'HS3_1295bp_Plotkin Declaration' spans from approximately position 4000 to 5200. The text below the diagram states: "The HS3 segment, represented by the blue box, is 1295 base pairs in length. It is bordered by the HindIII restriction enzyme site on the right and the BamHI restriction enzyme site on the left." Further analysis notes that the HS3 fragment in the HPV569 and BB305 vector is highly similar to and performs the same function as the HS3 fragment recited in the '179 Patent claims, based on publicly available information and general knowledge.</p> <p>The HS3 segment, represented by the blue box, is 1295 base pairs in length. It is bordered by the HindIII restriction enzyme site on the right and the BamHI restriction enzyme site on the left.</p> <p>Based on this analysis and other publicly available information, a POSA would understand that the HS3 fragment in the HPV569 and BB305 vector, although identified using different restriction enzymes, is nonetheless highly similar to and performing the same function as the HS3 fragment recited in the '179 Patent claims.</p> <p>For example, a POSA would understand based on publicly available information and general knowledge that HS3 fragment within the HPV569 vector is approximately 845 bp in length and located between SacI and PvuII restriction enzyme sites. In addition, a POSA would also know that the sequences of the HPV569 and BB305 vector are identical in the 2.7 kb <math>\beta</math>-globin LCR region. <i>See, e.g., Negre 2015, at 68 (“We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5’ HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of the 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta^{A-T87Q}</math>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS3 sequence for the BB305 vector onto the same human <math>\beta</math>-globin LCR region described in the Plotkin Declaration. Below is such a map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS3 fragment from the BB305 vector is in the middle of the image.</p>  <p>The diagram shows a horizontal double black line representing the human hemoglobin gene. Vertical lines indicate restriction enzyme cleavage sites. The map is divided into three main regions: HS4_BB (blue box), HS3_Plotkin (red box), and HS2_BB (blue box). The HS3_Plotkin region is centered around the HS3 fragment. Numerous restriction enzyme sites are labeled with their names and coordinates (e.g., SacI - BanII at 955, BstXI at 2352, PvuII at 5124, SmaI at 8224). The 'Start' and 'End' points are also indicated.</p> <p>NG_000007.1 HBB Ch 11 1-9520 bp w_BB and 179 Enzymes (1 - 9520) 9520 bp</p> <p>The double black line in this HS fragment map above represents a portion (9250 base pairs) of the human hemoglobin gene. This 9250 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '179 Patent (SnaBI, BstXI, HindIII, BamHI, Ban II) and in publicly available information regarding the HPV569 vector (SmaI, XbaI, SacI, PvuII, StuI and SpeI) are shown.</p> <p>A close-up view of this HS fragment map, which focuses on the middle region encompassing the HS3 fragment, is provided below:</p>

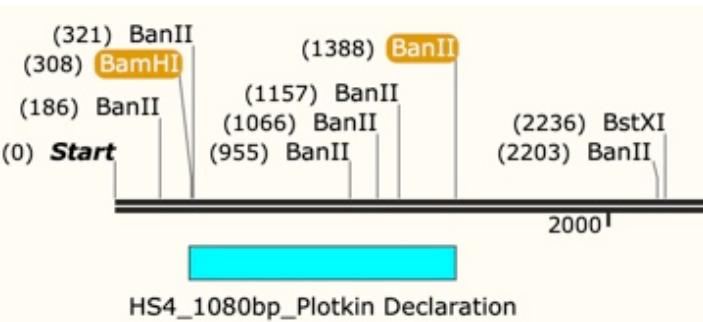
**EXHIBIT L**

U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p>The diagram illustrates the BB305 lentiviral vector's restriction map. Key features include:</p> <ul style="list-style-type: none"> <li><b>Left Side (4000 bp):</b> Labeled with BamHI, SpeI, SphI, KpnI, PstI, and SacI.</li> <li><b>Top (4628 bp):</b> Labeled with BanII.</li> <li><b>Middle (4365 bp):</b> Labeled with BanII.</li> <li><b>Bottom (4278 bp):</b> Labeled with SacI and BanII.</li> <li><b>Right Side (56 bp):</b> Labeled with BstXI.</li> <li><b>Bottom Right (6000 bp):</b> Labeled with BanI, SacI, SphI, and KpnI.</li> <li><b>HS3_Plotkin (Blue Box):</b> A fragment spanning from approximately 4000 bp to 5124 bp, containing PvuII sites at 5124 and 5149 bp, and a HindIII site at 5172 bp.</li> <li><b>HS3BB (Red Box):</b> A fragment spanning from approximately 5124 bp to 56 bp, containing PvuII sites at 5124 and 5149 bp, and a HindIII site at 5172 bp.</li> </ul>
		<p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS3 fragment within the BB305 vector is highly similar to the HS3 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the H32 sequence within the BB305 vector is equivalent to a “BamHI and HindIII HS3-spanning nucleotide fragment of said LCR”, (e.g., the HS3 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector.</p>
1.5	and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the claim limitation “and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the '179 Patent: through the incorporation of fragments of the HS2, HS3, and HS4 DNase I hypersensitive sites obtained from a human β-globin</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 Patent, the claimed vector “comprises a 3.2-kb portion <b>of a human <math>\beta</math>-globin locus control region (LCR) consisting essentially of 3 restriction fragments</b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the '221 Application. This declaration used the human <math>\beta</math>-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). <i>See Plotkin Declaration, ¶¶ 18 and 29.</i></p> <p>A POSA can take this same <math>\beta</math>-globin sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human <math>\beta</math>-globin LCR region. <i>See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</i></p> <p>The double black line in this HS fragment map represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '179 Patent are shown: (SnAB1, BstXI, HindIII, BamHI and Ban II). Note that</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, <b>only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange</b>. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.</p> <p>A close-up view of this HS fragment map, which focuses on the far left region encompassing the HS4 fragment, is provided below:</p>  <p>The diagram shows a horizontal line representing the BB305 vector genome. A blue box highlights the HS4 segment, labeled "HS4_1080bp_Plotkin Declaration". Above the genome, several restriction enzyme sites are marked with vertical lines and labels: (321) BanII, (308) BamHI, (186) BanII, (0) Start, (1388) BanII, (1157) BanII, (1066) BanII, (955) BanII, (2236) BstXI, and (2203) BanII. The positions of these sites are indicated by vertical lines along the genome line. The distance between the first and last labeled sites is marked as 2000 bp.</p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p> <p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS4 sequence for the BB305 vector onto the same human β-globin LCR region described in the Plotkin Declaration. Below is such an HS fragment map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS4 fragment from the BB305 vector is on the far left side of the map.</p> <p>NG_000007.1 HBB Ch 11 1-9520 bp w_BB and 179 Enzymes (1 - 9520) 9520 bp</p> <p>The double black line in this HS fragment map above represents a portion (9250 base pairs) of the human hemoglobin gene. This 9250 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '179 Patent (SnaBI, BstXI, HindIII, BamHI, Ban II) and by the restriction enzymes listed in publicly available information regarding the HPV569 vector (SmaI, XbaI, SacI, PvuII, StuI and SpeI) are shown.</p> <p>A close-up view of this HS fragment map, which focuses on the far left region of the map, encompassing the HS4 fragment, is provided below:</p>

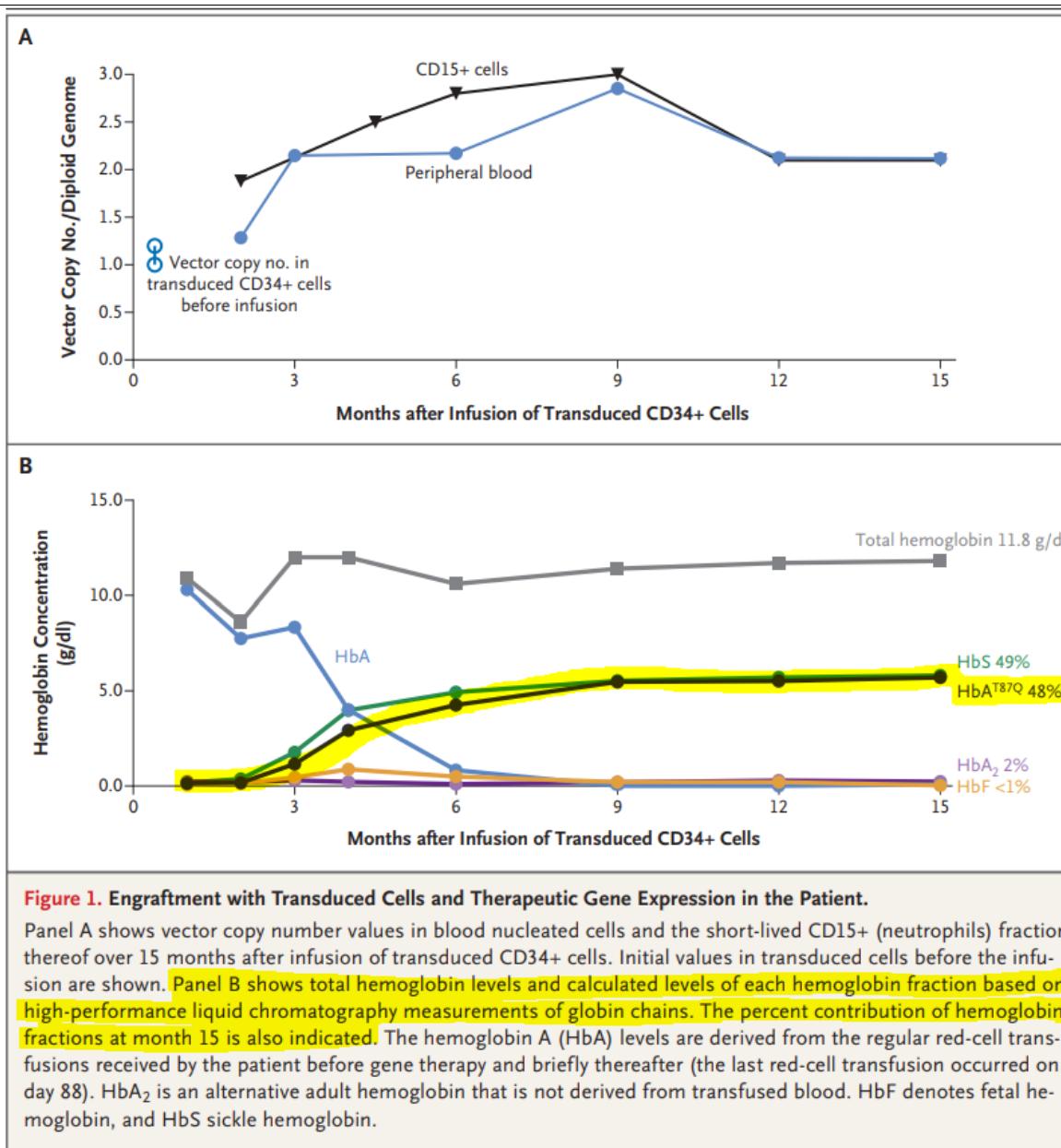
**EXHIBIT L**

U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p>The diagram illustrates the BB305 lentiviral vector structure. It features a horizontal black bar representing the vector backbone, with a red box labeled "HS4BB" indicating the location of the HS4 fragment. A blue box labeled "HS4_Plotkin" indicates the location of the HS4 fragment described in the Plotkin Declaration. Vertical lines represent restriction enzyme cleavage sites, each labeled with its corresponding restriction enzyme name and a reference number in parentheses. The sites are: (0) Start, (186) SacI - BanII, (308) BamHI, (321) SacI - BanII, (559) StuI, (955) SacI - BanII, (1066) BanII, (1157) BanII, (1388) BanII, (1708) SpeI, (2203) SacI - BanII, (2236) BstXI, (2352) XbaI, (2411) SphI, and (3251) (27). The total length of the vector is indicated as 2000.</p>
1.6	said vector providing expression of the globin in a mammal in vivo.	<p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS4 fragment within the BB305 vector is highly similar to the HS4 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the HS4 sequence within the BB305 vector is equivalent to the limitation “and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR,” (e.g., the HS4 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring <math>\beta</math>-globin gene within the vector.</p> <p>The BB305 vector meets the claim limitation where “said vector providing expression of the globin in a mammal in vivo.”</p> <p><u>Exemplary support:</u></p>

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U.S. Patent No. 7,541,179	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>See e.g.</i>, Ribeil et al., “Gene Therapy in a Patient with Sickle Cell Disease”, NEJM, 376(9): 848-855 (2017) (hereafter “Ribeil 2017”), which describes the results of gene therapy with the BB305 vector as follows:</p> <p><b><i>We describe our first patient treated with lentiviral vector-mediated addition of an antisickling β-globin gene into autologous hematopoietic stem cells.</i></b> Adverse events were consistent with busulfan conditioning. <b><i>Fifteen months after treatment, the level of therapeutic antisickling β-globin remained high (approximately 50% of β-like-globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease.</i></b> (Funded by Bluebird Bio and others; HGB-205 ClinicalTrials.gov number, NCT02151526.)”</p> <p>Ribeil 2017, at 848 (abstract).</p> <p><b><i>RESULTS</i></b> . . .</p> <p><b><i>Figure 1B shows production of HbA<sup>T87Q</sup>. . . . HbA<sup>T87Q</sup> levels also increased steadily (Fig. 1B) and red-cell transfusions were discontinued, with the last transfusion on day 88. Levels of HbA<sup>T87Q</sup> reached 5.5 g per deciliter (46%) at month 9 and continued to increase to 5.7 g per deciliter (48%) at month 15, with a reciprocal decrease in HbS levels to 5.5 g per deciliter (46%) at month 9 and 5.8 g per deciliter (49%) at month 15. Total hemoglobin levels were stable between 10.6 and 12.0 g per deciliter after post-transplantation month 6. . . .”</i></b></p> <p><i>Id.</i> at 850-51 (italics and emphasis added).</p>

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p><i>“In the current study, a high concentration of therapeutic HbA<sup>T87Q</sup> (ratio of HbA<sup>T87Q</sup> to HbS, approximately 1) was achieved.<sup>10,11</sup> HbA<sup>T87Q</sup> expression appears to be sufficient to suppress hemolysis, resulting in stable hemoglobin concentrations of 11 to 12 g per deciliter and major improvement in all measurable sickle cell disease-specific biologic markers and blocking sickle cell disease-related clinical events.<sup>20,21</sup></i></p> <p>Additional data on LentiGlobin treatment in sickle cell disease is currently being collected in HGB-206, a multicenter, phase 1/2 clinical study in the United States.<sup>19</sup> . . . <i>Outcomes in this patient provide further supportive evidence to our previously reported results of patients who underwent a similar ex vivo gene therapy procedure for β-thalassemia with the same BB305 vector<sup>22,23</sup> or the previous HPV569 vector.<sup>23,24</sup> In addition to the patient with sickle cell disease described here, under this same clinical protocol, 4 patients with transfusion-dependent β-thalassemia have received LentiGlobin BB305. These participants had no clinically significant complications and no longer require regular transfusions.<sup>22</sup> These findings are consistent with early results reported with 18 other patients with thalassemia who received LentiGlobin BB305 in clinical study HGB-204.<sup>23</sup> . . .”</i></p> <p>Ribeil 2017, at 854 (italics and emphasis added).</p>
23.0	A recombinant vector comprising	<p>The BB305 vector meets the limitation of “a recombinant vector comprising”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.0 supra.</i></p>
23.1	a nucleic acid encoding a functional globin operably linked to	<p>The BB305 vector has “a nucleic acid encoding a functional globin operably linked to”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.1 supra.</i></p>

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
23.2	a 3.2-kb nucleotide fragment which consists essentially of three nucleotide fragments obtainable from a human $\beta$ -globin LCR,	<p>The BB305 vector meets the limitation of “a 3.2-kb nucleotide fragment which consists essentially of three nucleotide fragments obtainable from a human <math>\beta</math>-globin LCR”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.2 supra.</i></p>
23.3	the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the limitation of “the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.3 supra.</i></p>
23.4	a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the limitation of “a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.4 supra.</i></p>
23.5	and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the limitation of “and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.5 supra.</i></p>

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
23.6	wherein the HS3-spanning nucleotide fragment and the HS4-spanning nucleotide fragment are adjacent to each other and the vector further comprises 2 GATA-binding sites at the junction between the HS3-spanning and HS4-spanning nucleotide fragments,	<p>The BB305 vector meets the limitation “wherein the HS3-spanning nucleotide fragment and the HS4-spanning nucleotide fragment are adjacent to each other and the vector further comprises 2 GATA-binding sites at the junction between the HS3-spanning and HS4-spanning nucleotide fragments”.</p> <p><u>Exemplary Support:</u></p> <p>During prosecution of the ’221 patent application that matured into the ’179 Patent, the Applicants defined “adjacent” as follows:</p> <p>“Claim 1 as currently amended recites that the three HS fragments are contiguous. According to the Random House Dictionary, contiguous is defined as: 1. touching; in contact, or 2. <b><i>in close proximity without actually touching; near.</i></b> The Random House Dictionary of the English Language (Stein, Ed.) Random House, New York, 1973, p. 316. For the first meaning, the definition is synonymous with bordering, adjoining and abutting; <b><i>for the second, the definition is synonymous with adjacent.</i></b> That the three fragments are contiguous is clear from Figs. 1 and 2. Amending the claim in this manner makes explicit a relationship that was already implicit in the subject matter as previously claimed. <b><i>As discussed in the text, here and in previous responses, the size sum of the three HS fragments rounds to 3.2 kb, meaning that the fragments are at least adjacent and could easily be rejoined.</i></b>”</p> <p>12/03/2008 Amendment After Final Office Action in US Patent Application No. 10/188,221, at p. 8 (italics and emphasis added).</p> <p>Based on publicly available information and their general knowledge, a POSA would understand that the BB305 vector comprises at least one GATA-binding site within its LCR region, and that this at least one GATA-binding site performs the same function in the same way to produce the same result as the two recited GATA-binding sites located “at the junction between the HS3-spanning and HS4-spanning nucleotide fragments”.</p>
23.7	said vector providing expression of the	The BB305 vector meets the claim limitation of “said vector providing expression of the globin in a mammal <i>in vivo</i> ”.

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U.S. Patent No. 7,541,179		BB305 lentiviral vector (hereafter “the BB305 vector”)
	globin in a mammal in vivo.	<u>Exemplary Support:</u> <i>See claim 1.6 supra.</i>

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# EXHIBIT M

## EXHIBIT M

U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
1.0	An isolated mammalian hematopoietic progenitor cell	<p>At least the CD34<sup>+</sup> hematopoietic stem cells (“CD34<sup>+</sup> HSCs”) described in Ribeil et al. (2017), <i>Gene Therapy in a Patient with Sickle Cell Disease</i>, <u>NEJM</u>, 376(9): 848-855 (hereafter, “Ribeil 2017”) meet the recited limitation of “[a]n isolated mammalian hematopoietic progenitor cell”.</p> <p><u>Exemplary support:</u></p> <p>Ribeil 2017 specifically describes human primary CD34<sup>+</sup> cells being isolated and then transduced with the BB305 vector. It states, for example:</p> <p><b><i>“Bone marrow was obtained twice from the patient to collect sufficient stem cells for gene transfer and backup</i></b> (6.2 x 10<sup>8</sup> per kilogram and 5.4x10<sup>8</sup> per kilogram, respectively, of total nucleated cells obtained). Both procedures were preceded by exchange transfusion, and bone marrow was obtained without clinical sequelae. Anemia was the only grade 3 adverse event reported during these procedures. <b><i>Bone marrow-enriched CD34+ cells were transduced with the LentiGlobin BB305 vector (see the Methods section in the Supplementary Appendix).</i></b><sup>13</sup> The mean vector copy numbers for the two batches of transduced cells were 1.0 and 1.2 copies per cell.”</p> <p>Ribeil 2017, at 849 (italics and emphasis added).</p> <p>A Person of Ordinary Skill in the Art (“POSA”) would understand, based on general knowledge, that the CD34<sup>+</sup> cells isolated from the patient’s bone marrow comprised a mixture of both HSCs and of hematopoietic progenitor cells (HPCs), which would have been isolated by various purification methods.</p> <p>For example, a 2014 scientific publication by Sidney <i>et al.</i> teaches that:</p> <p><b><i>“In clinical practice, CD34 expression is evaluated to ensure rapid engraftment in BM [bone marrow] transplants and can also be used as a selective marker in cell sorting to enrich a population of immature hematopoietic cells [46, 47]. Although sometimes assumed to be solely a stem cell marker, the detection of CD34 in BM or blood samples represents a hematopoietic stem/progenitor mix, of which the majority of cells are progenitor [44].”</i></b></p> <p>Sidney <i>et al.</i>, 2014, <i>Concise Review: Evidence for CD34 as a Common Marker for Diverse Progenitors</i>, Stem Cells, Vol. 32: 1380-1389 at 1381 (emphasis added) (citing reference 44 - Majeti <i>et al.</i>, 2007,</p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<i>Identification of a hierarchy of multipotent hematopoietic progenitors in human cord blood</i> , Cell Stem Cell, Vol. 1: 635-645).
1.1	or an isolated mammalian stem cell comprising	<p>At least the CD34<sup>+</sup> HSCs described in the Ribeil 2017 publication meet the recited limitation of “or an isolated mammalian stem cell comprising”.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.0, supra.</i></p> <p>A POSA would understand, based on the disclosures of Ribeil 2017 and general knowledge that the isolation of human CD34<sup>+</sup> cells prior to transduction with the BB305 vector (<i>e.g.</i>, as described on page 849 of Ribeil 2017) would necessarily also include the isolation of HSCs, which are a type of mammalian stem cells.</p>
1.2	a recombinant lentiviral vector	<p>At least the CD34<sup>+</sup> HSCs and hematopoietic progenitor cells (“HPCs”) described in Ribeil 2017 meet the recited limitation of comprising “a recombinant lentiviral vector” because they were transduced with the BB305 vector, which is “a recombinant lentiviral vector”.</p> <p><u>Exemplary support:</u></p> <p><i>See claims 1.0 and 1.1, supra.</i></p> <p>U.S. Patent No. 8058061 (“the ‘061 Patent”) defines “recombinant lentiviral vector” as follows:</p> <p>“As used in the specification and claims hereof, the term ‘recombinant lentiviral vector’ refers to an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation.”</p> <p>‘061 Patent, at col. 2: 39-43.</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>The publication by Negre et al., 2015, <i>Preclinical Evaluation of Efficacy and Safety of an Improved Lentiviral Vector for the Treatment of β-Thalassemia and Sickle Cell Disease</i>, <u>Current Gene Therapy</u>, Vol. 15, pp. 64-81 (hereafter, “Negre 2015”), describes the derivation of the BB305 vector from the lentiviral vector HPV569:</p> <p>“A previously published clinical trial demonstrated the benefit of autologous CD34<sup>+</sup> cells transduced with <b>a self-inactivating lentiviral vector (HPV569) containing an engineered β-globin gene (<math>\beta^{A-T87Q}</math>-globin)</b> in a subject with β-thalassemia major. <b>This vector has been modified to increase transduction efficacy without compromising safety.</b> . . . <b>This comprehensive efficacy and safety data provided the basis for initiating two clinical trials with this second generation vector (BB305) in Europe and in the USA in patients with β-thalassemia major and sickle cell disease.</b></p> <p>...</p> <p><b>LentiGlobin BB305 Lentiviral Vector Titer and In vitro Transduction Efficiency</b></p> <p><b>We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta^{A-T87Q}</math>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors[,] and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remained unchanged.”</b></p> <p>Negre 2015, at 64 (abstract) and 68 (emphasis and italics added).</p> <p>Ribeil 2017 is a scientific publication that describes the results of a clinical trial involving the LentiGlobin BB305 vector, which is described as a “self-inactivating lentiviral vector” that “encodes the human HBB variant <math>\beta^{A-T87Q}</math>” for use in transducing hematopoietic stem cells and hematopoietic progenitor cells so that they might produce human globin protein. Ribeil 2017, at 849. Ribeil 2017 provides the following diagram demonstrating the structure of the BB305 vector:</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><b><u>FIGURE S1. DIAGRAM OF BB305 VECTOR</u></b></p> <p>See <i>id.</i> at 10 (Figure S1 in Supplementary Appendix).</p> <p>Ribeil 2017 also describes the construction of the BB305 vector and the fact that it represents a modified version of the HPV569 lentiviral vector:</p> <p>“METHODS</p> <p>Additional Detail on Study Conduct.</p> <p><i>The original HPV569 vector and packaging plasmids were designed by Dr. Leboulch and colleagues and further modified in collaboration with the study sponsor, and clinical-grade BB305 vector manufacturing was performed by bluebird bio.</i> Dr. Cavazzana is principal investigator of the study, performed pre-clinical and clinical laboratory work, and oversees patient care, laboratory work and drug product manufacturing at Necker Hospital. Dr. Leboulch was the study’s scientific director.”</p> <p>Ribeil 2017, at page 4 (Supplementary Appendix, Methods section).</p> <p>A POSA would know, based on the disclosures of Ribeil 2017 and general knowledge, plus the similarity between the structures and DNA sequences of the HPV549 and BB305 vectors, that both are recombinant lentiviral vectors.</p>
1.3 which comprises a nucleic acid encoding a functional globin	<p>The following recombinant vector comprises “a nucleic acid encoding a functional globin operably linked to”: BB305.</p> <p><u>Exemplary support:</u></p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
operably linked to	<p>“The term ‘functional globin gene’ refers to a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene.” ’179 Patent, at col. 2:41-45.</p> <p>“The functional globin gene may encode a wild-type globin appropriate for a mammalian individual to be treated, or it may be a mutant form of globin, preferably one which provides for superior properties, for example superior oxygen transport properties. <b><i>The functional globin gene includes both exons and introns, as well as globin promoters and splice donors/acceptors.</i></b> Suitably, the globin gene may encode α-globin, β-globin, or γ-globin. β-globin promoters may be sued [sic] with each of the globin genes.” <i>Id.</i>, at col. 2:45-53 (italics and emphasis added).</p> <p>As shown in Figure 1A of Negre 2015 (reproduced below), the BB305 vector encodes a functional globin, as it contains within it β-globin exons 1 to 3, β-globin introns 1 and 2, a β-globin promoter and enhancer, and DNase I hypersensitivity sites 2, 3 and 4 (HS2, HS3 and HS4). All of these features have been highlighted in yellow in Figure 1A:</p> <p><b>A</b></p> <p><b>Fig. (1).</b> <i>In vitro evaluation of LentiGlobin lentiviral vectors. A) Diagram of the LentiGlobin HPV569 and BB305 lentiviral vectors. The 3' β-globin enhancer, the 372 base pairs (bp) IVS2 deletion in intron</i></p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p><i>2 (triangle), the <math>\beta^{A-T87Q}</math> mutation (ACA [Thr] to CAG [Gln]) and DNase I hypersensitive sites (HS) 2, HS3, and HS4 of the human <math>\beta</math>-globin locus control region (LCR) are indicated.</i> Safety modifications including the 400 bp deletion in the U3 of the right HIV LTR, the rabbit <math>\beta</math>-globin polyA signal and the 2 x 250 bp cHS4 chromatin insulators are indicated. <math>\beta</math>p, human <math>\beta</math>-globin promoter; cPPT/flap, central polypurine tract; HIV LTR, human immunodeficiency type-1 virus long-terminal repeat; ppt, polypurine tract; RRE, Rev-responsive element; <math>\Psi^+</math>, packaging signal. . . .”</p> <p>Negre 2015, at 66 (Figure 1 and legend) (italics and emphasis added).</p> <p>A POSA, reviewing the Negre 2015 publication in light of their general knowledge, would understand that the BB305 vector contains a nucleic acid encoding a functional human <math>\beta</math>-globin gene.</p>
1.4	a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human $\beta$ -globin locus	<p>The BB305 vector meets the claim limitation of “a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human <math>\beta</math>-globin locus control region (LCR)”.</p> <p><u>Exemplary support:</u></p> <p>The BB305 vector performs the same function (enhancing <math>\beta</math>-globin expression beyond levels previously achieved), in the same way (to obtain the same result) as the vectors claimed in the ’061 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human <math>\beta</math>-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>A POSA would read the information in May et al., <i>Therapeutic haemoglobin synthesis in <math>\beta</math>-thalassemic mice expressing lentivirus-encoded human <math>\beta</math>-globin</i>, Nature, Vol 406, pp. 82-86 (July 6, 2000) (hereafter “May 2000”) and the prosecution history for US Patent Application No. 10/188221<sup>1</sup>, and understand them as indicating that the new vectors described therein (and claimed in the ’179 Patent) occupied a middle ground between the prior art</p>

<sup>1</sup> US 8058061 claims priority to the patent application 10/188221 (“the ’221 Application”), which issued as US 7541179 (“the ’179 Patent”). Accordingly, this claim chart includes references to the specification of the ’179 Patent and to the prosecution history of the ’221 Application, as it also sheds light on the meaning of the ’061 Patent claims.

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
control region (LCR),	<p>vectors that contained minimal LCRs and the prior art vectors that contained much larger LCRs. For example, May 2000 states:</p> <p>“Incorporation of small elements spanning DNase HS2, HS3 and HS4 into viral vectors increases β-globin expression in mouse erythroleukaemia (MEL) cells<sup>9,10</sup>. However, low-level expression, strong position effects and transcriptional inactivation are still observed in bone marrow chimaeras<sup>5,11</sup>. Studies in transgenic mice<sup>12</sup> and deletional analyses<sup>13</sup> support the view that coordinated interaction of several genetic elements including the LCR is required for physiologic β-globin gene expression<sup>12-15</sup>. <b>We therefore thought that incorporation of large elements spanning HS2, HS3 and HS4<sup>16-18</sup> in a vector might enhance β-globin expression beyond levels previously achieved using arrayed minimal core elements<sup>5,9-11</sup>, and thus might diminish position effects and vector silencing.</b> The efficient transduction of large genomic fragments using onco-retroviral vectors has proved to be severely curtailed by splicing and other alterations affecting the stability of the recombinant genomes<sup>9,10,16</sup>. Here we report how these problems may be overcome by using vectors derived from human immunodeficiency virus 1, a retrovirus that has the ability to regulate packaging of unspliced viral genomes. We constructed two recombinant lentiviruses carrying β-globin transcription units (Fig. 1a, b). RNS1 contains a minimal LCR comprising previously tested core elements of HS2, HS3 and HS4 (ref. 9).” May 2000, at p. 82 (italics added).</p> <p>This contention is supported by multiple statements in the prosecution history of the ’221 Application. For example, the Applicants stated:</p> <p>“The nature of the invention identifies the field of the endeavor - here a recombinant vector for treating hemoglobinopathies by expressing a functional globin <i>in vivo</i> using the claimed 3.2-kb portion of a human β-globin LCR. As an aside, . . . the Examiner characterized the three fragments in the LCR as ‘essential elements from the β-globin LCR.’ Applicants wish to clarify this remark as it is not a term of art and is somewhat misleading. <i>The literature describes core HS sites as small fragments, and these core sequences might be considered as ‘essential’ or ‘minimal’ since they are the smallest fragments that can effect globin expression. In point of fact, the present invention resides in having more than these small core sequences, namely, the invention resides in having the larger, specific HS-containing fragments in the vector and obtaining a level of globin expression not previously possible in vivo.</i>”</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>09/12/2007 Rule 116 Amendment and Response for US Patent Application No. 10/188221, at p. 13 (hereafter “09/12/2007 Response”) (italics and emphasis added).</p> <p>In fact, Applicants specifically pointed out to the United States Patent and Trademark Office (“USPTO”) Examiner for the ’221 Application that prior art vectors had human <math>\beta</math>-globin LCR fragments that ranged in size from very large (20 kb) to very small (1 kb):</p> <p>“As mentioned, the human <math>\beta</math>-globin LCR is a 20-30 kb region extending upstream from the start of the <math>\epsilon</math>-globin gene. The region has been extensively analyzed and the scientific literature reports a variety of expression studies with a 20-kb ‘minilocus,’ a 6.5-kb [‘]microlocus’ and a 1-kb fragment with core DNase I hypersensitive site[s].”</p> <p>09/12/2007 Response, at p. 10 (internal citations omitted).</p> <p>The Applicants distinguished their claims from the prior art by contending that, to their knowledge, “no previous studies have been conducted with a 3.2-kb portion of a human <math>\beta</math>-globin LCR as claimed herein.” <i>Id.</i></p> <p>Because the descriptions of the core sequences for the HS2, HS3 and HS4 regions were known in the prior art, the Applicants asserted that not only should one assume the DNase hypersensitivity-spanning fragments “<i>are at least as big as their corresponding core sequences</i>”, but also that a POSA would “<i>know[], in fact, that they must be larger</i>”. 09/12/2007 Declaration of Jason W. Plotkin Under 37 C.F.R. §1.132 (hereafter, “Plotkin Declaration”), at ¶ 36 (italics added), as submitted with 09/12/2007 Response.</p> <p>In particular, a POSA would know that incorporation of only the “core” LCR fragments resulted in vectors with low viral titers that were “highly unstable with multiple rearrangements of the transferred proviral structures”. <i>See Negre et al., 2016, Gene Therapy of the <math>\beta</math>-Hemoglobinopathies by Lentiviral Transfer of the <math>\beta</math>A(T87Q)-Globin Gene, Human Gene Therapy, Vol. 27, No. 2, 148- 165 at 154</i> (hereafter, “Negre 2016”) (internal citations omitted). In addition, a POSA would have been aware that “[r]educing the size of the LCR to minimal elements is unsatisfactory as <math>\beta</math>-globin expression levels are too low.” <i>Id.</i> (citing references from 1992-1997); <i>see also</i>, May 2000, at p. 82. Accordingly, a POSA would understand that the claimed vectors needed to have an HS2-HS3-HS4 region that was bigger than 1 kb (<i>i.e.</i>, had more than the minimal core HS sequences).</p>

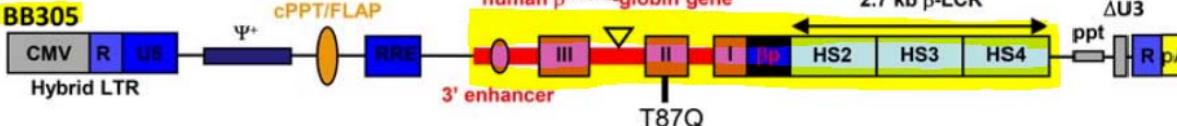
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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>In addition to setting a lower 1 kb boundary, the Applicants for the ’221 Application provided a flexible upper boundary of approximately 3.2 kb for the combined HS-spanning nucleotide fragments when they argued to the USPTO that:</p> <p>“The simple fact that the combination of the three HS-spanning fragments is 3.2 kb partially (and significantly) closes this aspect of the present claim, <i>qualifies its size and thus provides the boundaries for ascertaining the elements excluded by use of ‘consisting essentially of’ as the transitional phrase</i>. For example, any additional nucleotides added to the 3.2 kb fragment that cause the fragment to exceed 3.2 kb, would alter a basic and novel property of the invention. As <i>Applicants have exhaustively established on the record, the combined size of the three HS-spanning fragments so closely approximates 3.2 kb, that the number of additional nucleotides that could be added to (or removed from) this fragment is relatively few and non-material</i>. <i>For example, the types of non-material nucleotide changes that can be accommodated are . . . adding a small linker to provide or change a restriction site, or making any other minor change to the sequence that does not alter the functionality of the fragment in driving globin expression, including changes at the ends of or at the junction points of the fragments</i>. All such changes are well known in the art and would be readily contemplated, accomplished and analyzed by skilled artisans. <i>However, none of these non-material changes rises to the level of the fragments taught by Ryan or Antoniu. . . . Ryan shows only a 30-kb and a 22-kb recombinant nucleotide fragment that contain at least HS2, HS3, and HS4. . . . Antoniu show[s] only a single 5.5 kb nucleotide fragment that contains HS2, HS3 and HS4. Based on size, the Ryan and Antoniu fragments clearly differ from the 3.2 kb fragment of Claim 1.</i></p> <p>Further, based on nucleotide composition and arrangement of the HS fragments (i.e., which pieces of the LCR are present), <i>neither Ryan nor Antoniu shows any fragment that combines the recited HS2-, HS3- and HS4-spanning fragments in contiguity into a single 3.2-kb fragment as claimed in present Claim 1</i>. Ryan’s fragments are single, large restriction fragments from the LCR encompassing all 5 HS sites in their natural order and sequence context. Antoniu fragments combine various restriction fragments which are larger and distinct from those claimed by Applicants. Merely because the three HS fragments that Applicants have identified are within the sequence of the Ryan and Antoniu fragments does not mean that those references “encompass” the claimed 3.2-kb fragment and thereby anticipate the present invention. <i>The actual combination must be demonstrated in these references and it is not, as evidenced by Applicants’ use of ‘consisting essentially of’ as the transitional phrase, along with bounding this operable LCR fragment at</i></p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>3.2 kb, which, therefore, serve to distinguish the claimed invention from Ryan and Antoniu as well as establish the basic and novel properties of this nucleotide fragment.</i></p> <p>12/03/2008 Amendment and Response After Final Office Action for the ’221 Application, at pp. 9-10 (italics and emphasis added).</p> <p>Thus, a POSA would understand, based on these comments in the prosecution history for the ’221 Application, that the claimed vectors in the ’179 Patent can encompass vectors with LCR regions that differ in size and in sequence identity from the 3.2 kb LCR fragment identified in the Plotkin Declaration, provided that these differences do not bring the LCR fragment to a size that is much greater than 3.2 kb, or materially alter its function.</p> <p>“As apparent from the reference sequence, and as known in the art, <i>the three fragments that form the 3.2-kb portion of the LCR are assembled from non-contiguous portions of the LCR</i>. In this regard, it should be recognized that these fragments can be joined in either 5’-3’ or 3’-5’ orientation using any of numerous techniques known to those of skill in the art to provide further vector examples. <i>Once assembled into a vector, the fragments need not be cleavable nor must the entire restriction recognition site be present</i>. For example, one skilled in the art will readily [sic] appreciate that the full restriction site might not be present if the fragment is blunt-ended before ligation, yet it may be present if the cut site is filled before ligation.”</p> <p>09/12/2007 Response, at p. 15 (italics and emphasis added).</p> <p>A POSA would also readily understand that sequence for a human gene, particularly a gene such as human β-globin, will change over time as sequencing techniques and technologies improve. Applicants admitted that the “globin genes were among the first ever sequenced at the nucleotide level.” 9/12/2007 Response, at p. 7. The Applicants also admitted in 2007 that “When accessing NG_000007 at present, one obtains version 3, which in relevant part includes an additional approximately 9kb upstream of the version 1. <i>Hence the numbering of the nucleotides is offset between the versions, and can be further slightly offset by polymorphisms and minor variations.</i>” <i>Id.</i> (italics and emphasis added). This, combined with the fact that claim 1 of the ’061 Patent recites “a” human β-globin LCR rather than “the” human β-globin LCR, would indicate to a POSA that it is the size of the HS-spanning fragments that is most important, and sequence variation in the HS-spanning LCR fragment of the claimed vectors is permitted, provided that it does not substantially alter the vector’s properties.</p> <p>Figure 1A of Negre 2015 is reproduced in part below with its globin-related elements highlighted in yellow.</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	 <p><b>“Fig. (1). In vitro evaluation of LentiGlobin lentiviral vectors. A) Diagram of the LentiGlobin HPV569 and BB305 lentiviral vectors. The 3' β-globin enhancer, the 372 base pairs (bp) IVS2 deletion in intron 2 (triangle), the β<sup>A-T87Q</sup> mutation (ACA [Thr] to CAG [Gln]) and DNase I hypersensitive sites (HS) 2, HS3, and HS4 of the human β-globin locus control region (LCR) are indicated. Safety modifications including the 400 bp deletion in the U3 of the right HIV LTR, the rabbit β-globin polyA signal and the 2 x 250 bp cHS4 chromatin insulators are indicated. βp, human β-globin promoter; cPPT/flap, central polypyrimidine tract; HIV LTR, human immunodeficiency type-1 virus long-terminal repeat; ppt, polypyrimidine tract; RRE, Rev-responsive element; Ψ<sup>+</sup>, packaging signal. . . .”</b></p> <p>Negre 2015, at 66 (Figure 1 and legend) (italics and emphasis added).</p> <p>Based on Figure 1A of Negre 2015, as well as their general knowledge, a POSA would readily understand that the BB305 vector encodes a mutated (T87Q) human β-globin gene operably linked to a 2.7 kb human β-globin LCR region.</p> <p>A POSA would further understand that the BB305 vector, with its 2.7 kb human β-globin LCR region, performs the same function as the vectors claimed in the '061 Patent (enhancing β-globin expression beyond levels previously achieved) in the same way: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>A POSA would also know that the BB305 vector achieves the same result as the vectors claimed in the '061 Patent – the correction of hemoglobinopathies in animal or human cells. For example, the Negre 2015 publication states that the BB305 vector was able to correct a β-thalassemic phenotype in mice:</p> <p><b>“In conclusion, overall phenotype correction of β-thalassemic mice was observed with both LentiGlobin HPV569 and BB305 lentiviral vectors with no alteration of bone marrow homeostasis in the primary transplant animals. . . . Clinical trials of BB305 are underway in both β-thalassemia and sickle cell disease</b></p>

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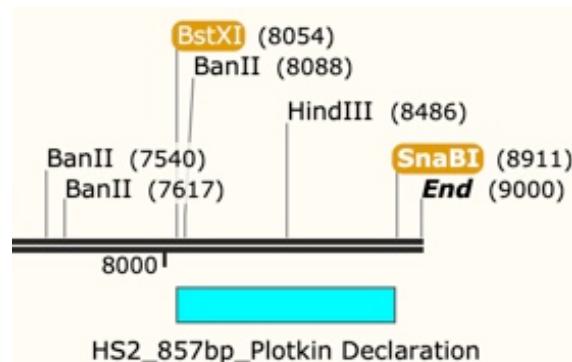
U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p>in Europe and for β-thalassemia in the USA. <i>Preliminary clinical results showing the advantage of the new Lentiglobin BB305 lentiviral vector over the previous HPV569 vector in β-thalassemia patients were reported at the 2014 annual meeting of the European Hematology Association and the 2014 annual meeting of the American Society of Hematology . . .</i></p> <p>Negre 2015, p. 78 (italics and emphasis added).</p>
1.5	the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the claim limitation of “the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the '061 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 Patent, the claimed vector “comprises a 3.2-kb portion of <b>a human β-globin locus control region (LCR) consisting essentially of 3 restriction fragments</b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the '221 Application. This declaration used the human β-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). See Plotkin Declaration, ¶¶ 18 and 29.</p> <p>A POSA can take this same β-globin reference sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human β-globin LCR region. See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)		
	<p>The diagram illustrates the BB305 lentiviral vector's genome with three horizontal bars representing different restriction digestions:</p> <ul style="list-style-type: none"> <li><b>HS4_1080bp_Plotkin Declaration:</b> Labeled at position 0 (Start) and 2000.</li> <li><b>HS3_1295bp_Plotkin Declaration:</b> Labeled at position 4000 and 6000.</li> <li><b>HS2_857bp_Plotkin Declaration:</b> Labeled at position 8000 and End (9000).</li> </ul> <p>Key restriction enzyme sites and their coordinates are highlighted in orange boxes:</p> <ul style="list-style-type: none"> <li><b>BamHI:</b> (308), (3877)</li> <li><b>BstXI:</b> (2236), (5656)</li> <li><b>HindIII:</b> (1388), (3572), (8486)</li> <li><b>BanII:</b> (321), (186), (1157), (1066), (955), (2203), (3714), (3573), (3529), (4278), (4628), (5172), (5998), (6084), (6110), (6158), (6733), (7540), (7617)</li> <li><b>SnaBI:</b> (8054), (8088), (8911)</li> </ul> <p>A double black line spans from position 0 to 9000, representing the human hemoglobin gene.</p> <p style="text-align: center;"><b>NG_000007.1 HBB on CH11 (1 - 9000) HS4</b></p>		

The double black line in this HS fragment map above represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '061 Patent are shown: (SnaBI, BstXI, HindIII, BamHI and Ban II). Note that although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, **only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange**. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.

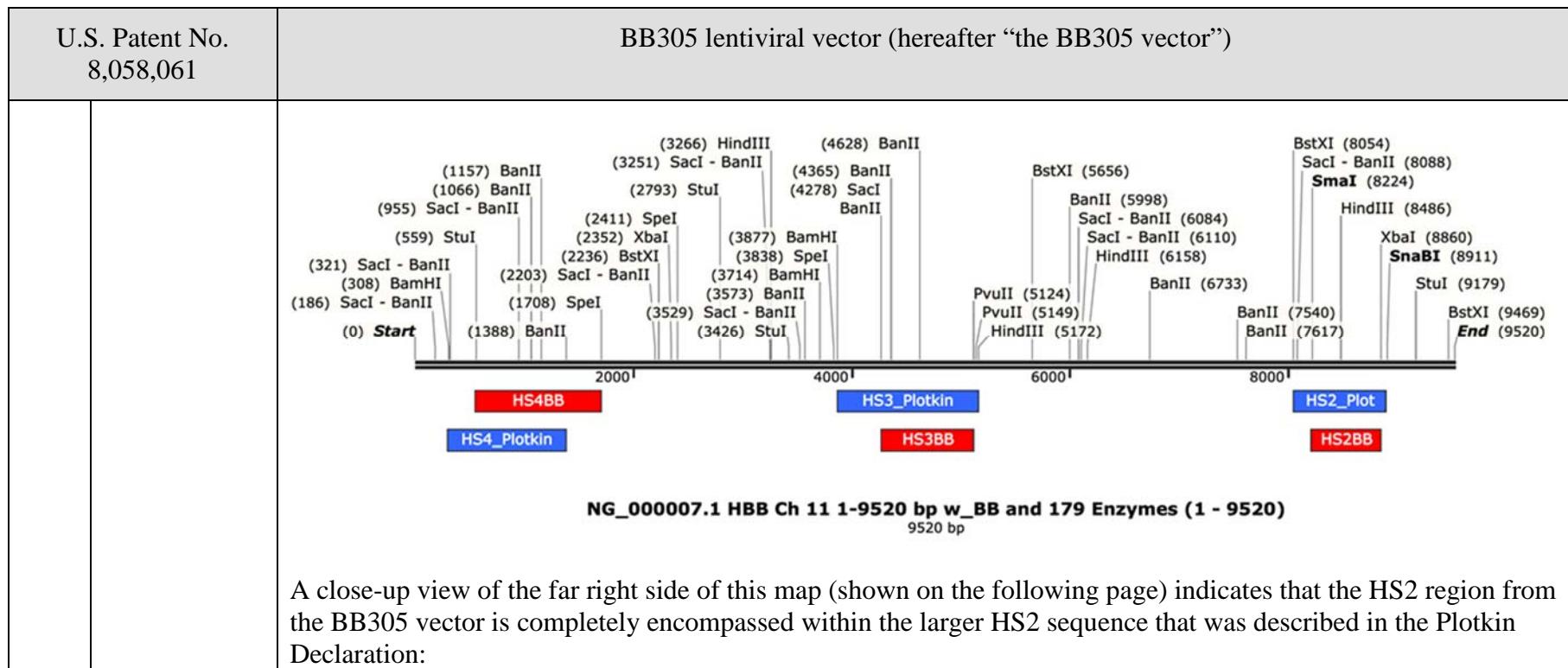
A close-up view of this HS fragment map, which focuses on the far right region encompassing the HS2 fragment, is provided below:



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	<p>Based on this analysis and other publicly available information, a POSA would understand that the HS2 fragment in the HPV569 and BB305 vector, although identified using different restriction enzymes, is nonetheless highly similar to and performing the same function as the HS2 fragment recited in the '061 Patent claims.</p> <p>For example, a POSA would understand based on publicly available information and general knowledge that HS2 fragment within the HPV569 vector is approximately 644 bp in length and located between SmaI and XbaI restriction enzyme sites. In addition, a POSA would also know that the sequences of the HPV569 and BB305 vector are identical in the 2.7 kb <math>\beta</math>-globin LCR region. <i>See, e.g., Negre 2015, at 68 (“We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of the 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta^{A-T87Q}</math>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p> <p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS2 sequence for the BB305 vector onto the same human <math>\beta</math>-globin LCR region described in the Plotkin Declaration. Below is such a map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS2 fragment from the BB305 vector is on the far right-hand side image.</p>

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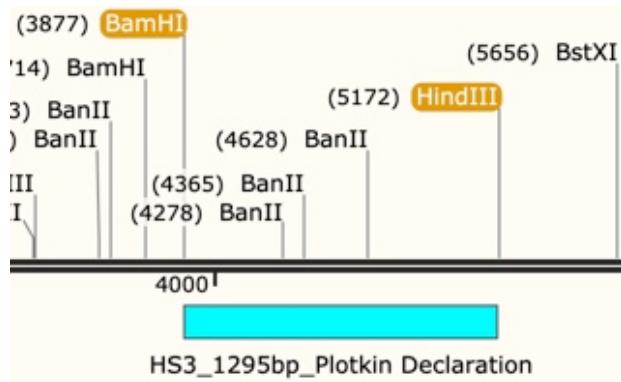
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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)	
	<p>BstXI (8054) SacI - BanII (8088) <b>SmaI</b> (8224) HindIII (8486) XbaI (8860) <b>SnaBI</b> (8911) StuI (9179) BstXI (9469) <b>End</b> (9520)</p> <p>8000</p> <p>HS2_Plot</p> <p>HS2BB</p>	
1.6 a BamHI and HindIII, HS3- spanning nucleotide fragment of said LCR,	<p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS2 fragment within the BB305 vector is highly similar to the HS2 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the HS2 sequence within the BB305 vector is equivalent to a “SnaBI and BstXI HS2-spanning nucleotide fragment of said LCR”, (e.g., the HS2 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector.</p> <p>The BB305 vector meets the claim limitation of “a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p>	

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U.S. Patent No. 8,058,061	<b>BB305 lentiviral vector (hereafter “the BB305 vector”)</b>
	<p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the '061 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 Patent, the claimed vector “comprises a 3.2-kb portion <b>of a human β-globin locus control region (LCR) consisting essentially of 3 restriction fragments</b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the '221 Application. This declaration used the human β-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). <i>See Plotkin Declaration, ¶¶ 18 and 29.</i></p> <p>A POSA can take this same β-globin sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human β-globin LCR region. <i>See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</i></p> <p style="text-align: center;"><b>NG_000007.1 HBB on CH11 (1 - 9000) HS4</b></p> <p>The double black line in this HS fragment map above represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA.</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '061 patent are shown: (SnaBI, BstXI, HindIII, BamHI and Ban II). Note that although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, <b><u>only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange</u></b>. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.</p> <p>A close-up view of this HS fragment map, which focuses on the middle region encompassing the HS3 fragment, is provided below:</p>  <p>The diagram shows a horizontal line representing a 4000bp region. Vertical lines indicate restriction sites for BamHI, BanII, HindIII, and BstXI. A blue box highlights the HS3 segment, labeled "HS3_1295bp_Plotkin Declaration".</p> <p>The HS3 segment, represented by the blue box, is 1295 base pairs in length. It is bordered by the HindIII restriction enzyme site on the right and the BamHI restriction enzyme site on the left.</p> <p>Based on this analysis and other publicly available information, a POSA would understand that the HS3 fragment in the HPV569 and BB305 vector, although identified using different restriction enzymes, is nonetheless highly similar to and performing the same function as the HS3 fragment recited in the '061 Patent claims.</p> <p>For example, a POSA would understand based on publicly available information and general knowledge that HS3 fragment within the HPV569 vector is approximately 845 bp in length and located between SacI and PvuII restriction enzyme sites. In addition, a POSA would also know that the sequences of the HPV569 and BB305 vector are identical in the 2.7 kb β-globin LCR region. <i>See, e.g., Negre 2015, at 68 (“We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of the 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in</i></p>

## EXHIBIT M

U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta^{A-T87Q}</math>-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p> <p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS3 sequence for the BB305 vector onto the same human <math>\beta</math>-globin LCR region described in the Plotkin Declaration. Below is such a map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS3 fragment from the BB305 vector is in the middle of the image.</p> <p>The double black line in this HS fragment map above represents a portion (9250 base pairs) of the human hemoglobin gene. This 9250 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '061 Patent (SnaBI,</p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>BstXI, HindIII, BamHI, Ban II) and in publicly available information regarding the HPV569 vector (SmaI, XbaI, SacI, PvuII, StuI and SpeI) are shown.</p> <p>A close-up view of this HS fragment map, which focuses on the middle region encompassing the HS3 fragment, is provided on the following page:</p> <p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS3 fragment within the BB305 vector is highly similar to the HS3 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the HS3 sequence within the BB305 vector is equivalent to a “BamHI and HindIII HS3-spanning nucleotide fragment of said LCR”, (e.g., the HS3 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector.</p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
1.7	and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,	<p>The BB305 vector meets the claim limitation “and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR”.</p> <p><u>Exemplary Support:</u></p> <p>The BB305 vector performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way as the claimed vectors of the '061 Patent: through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined.</p> <p>As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 Patent, the claimed vector “comprises a 3.2-kb portion <b><i>of a human β-globin locus control region (LCR) consisting essentially of 3 restriction fragments</i></b>. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment’s end is identified by particular restriction enzyme recognition sites (listed in 5’ to 3’ order).” 09/12/2007 Response, at p. 6 (italics and emphasis added).</p> <p>The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the inventor’s labs (Dr. Michel Sadelain), which detailed how one could “identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001,” which is the earliest filing date of the '221 Application. This declaration used the human β-globin reference DNA sequence NG000007.1 (hereafter, “NG7.1”). <i>See Plotkin Declaration, ¶¶ 18 and 29.</i></p> <p>A POSA can take this same β-globin sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin’s Declaration onto its human β-globin LCR region. <i>See Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:</i></p>

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U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)		
	<p>HS4_1080bp_Plotkin Declaration      HS3_1295bp_Plotkin Declaration      HS2_857bp_Plotkin Declaration</p> <p>NG_000007.1 HBB on CH11 (1 - 9000) HS4</p> <p>The double black line in this HS fragment map represents a portion (9000 base pairs) of the human hemoglobin gene. This 9000 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '061 Patent are shown: (SnaBI, BstXI, HindIII, BamHI and Ban II). Note that although this 9000 bp portion of DNA contains multiple restriction enzyme recognition sites, <b>only the six restriction enzyme recognition sites recited in claim 1 are highlighted in orange</b>. The size of each HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence.</p> <p>A close-up view of this HS fragment map, which focuses on the far left region encompassing the HS4 fragment, is provided below:</p> <p>HS4_1080bp_Plotkin Declaration</p>		

## EXHIBIT M

U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p>The HS4 segment, represented by the blue box, is 1080 base pairs in length. It is bordered by the BanII restriction enzyme site on the right and the BamHI restriction enzyme site on the left.</p> <p>Based on this analysis and other publicly available information, a POSA would understand that the HS4 fragment in the HPV569 and BB305 vector, although identified using different restriction enzymes, is nonetheless highly similar to and performing the same function as the HS4 fragment recited in the '061 Patent claims.</p> <p>For example, a POSA would understand based on publicly available information and general knowledge that the HS4 fragment within the HPV569 vector is approximately 1153 bp in length and located between StuI and SpeI restriction enzyme sites. In addition, a POSA would also know that the sequences of the HPV569 and BB305 vector are identical in the 2.7 kb <math>\beta</math>-globin LCR region. <i>See, e.g., Negre 2015, at 68 (“We redesigned the LentiGlobin HPV569 lentiviral vector by replacing the 5' HIV U3 LTR promoter/enhancer with the CMV promoter/enhancer. We also removed the 2 copies of the 250 base pair (bp) core chicken hypersensitivity site 4 (cHS4) insulators imbedded in the SIN U3 LTR of LentiGlobin HPV569, which resulted in the construction of LentiGlobin BB305 lentiviral vector (Fig. 1A). The sequences of the integrated provirus containing the <math>\beta</math>A-T87Q-globin gene expression cassette[,] the cPPT/cTS, RRE, and SIN U3 are identical in both lentiviral vectors and the internal globin promoter together with the LCR sequence driving the transgene expression exclusively in the erythroid lineage, remain unchanged.”).</i></p> <p>Accordingly, a POSA, using this publicly available information and general knowledge, would be able to physically map the HS4 sequence for the BB305 vector onto the same human <math>\beta</math>-globin LCR region described in the Plotkin Declaration. Below is such an HS fragment map, with the HS sequences from the Plotkin Declaration in blue, and the HS sequences from the BB305 vector in red. The HS4 fragment from the BB305 vector is on the far left side of the map.</p>

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U.S. Patent No. 8,058,061	<b>BB305 lentiviral vector (hereafter “the BB305 vector”)</b> <p><b>NG_000007.1 HBB Ch 11 1-9520 bp w_BB and 179 Enzymes (1 - 9520)</b> 9520 bp</p>
	<p>The double black line in this HS fragment map above represents a portion (9250 base pairs) of the human hemoglobin gene on chromosome 11. This 9250 bp portion of the human beta-globin gene contains within it many restriction enzyme recognition sites, which are DNA sequences where a specific restriction enzyme will bind and then cut the DNA. In the map above, only the sites recognized by the restriction enzymes cited in the claims of the '061 Patent (SnaBI, BstXI, HindIII, BamHI, Ban II) and by the restriction enzymes listed in publicly available information regarding the HPV569 vector (SmaI, XbaI, SacI, PvuII, StuI and SpeI) are shown.</p> <p>A close-up view of this HS fragment map, which focuses on the far left region of the map, encompassing the HS4 fragment, is provided below:</p>

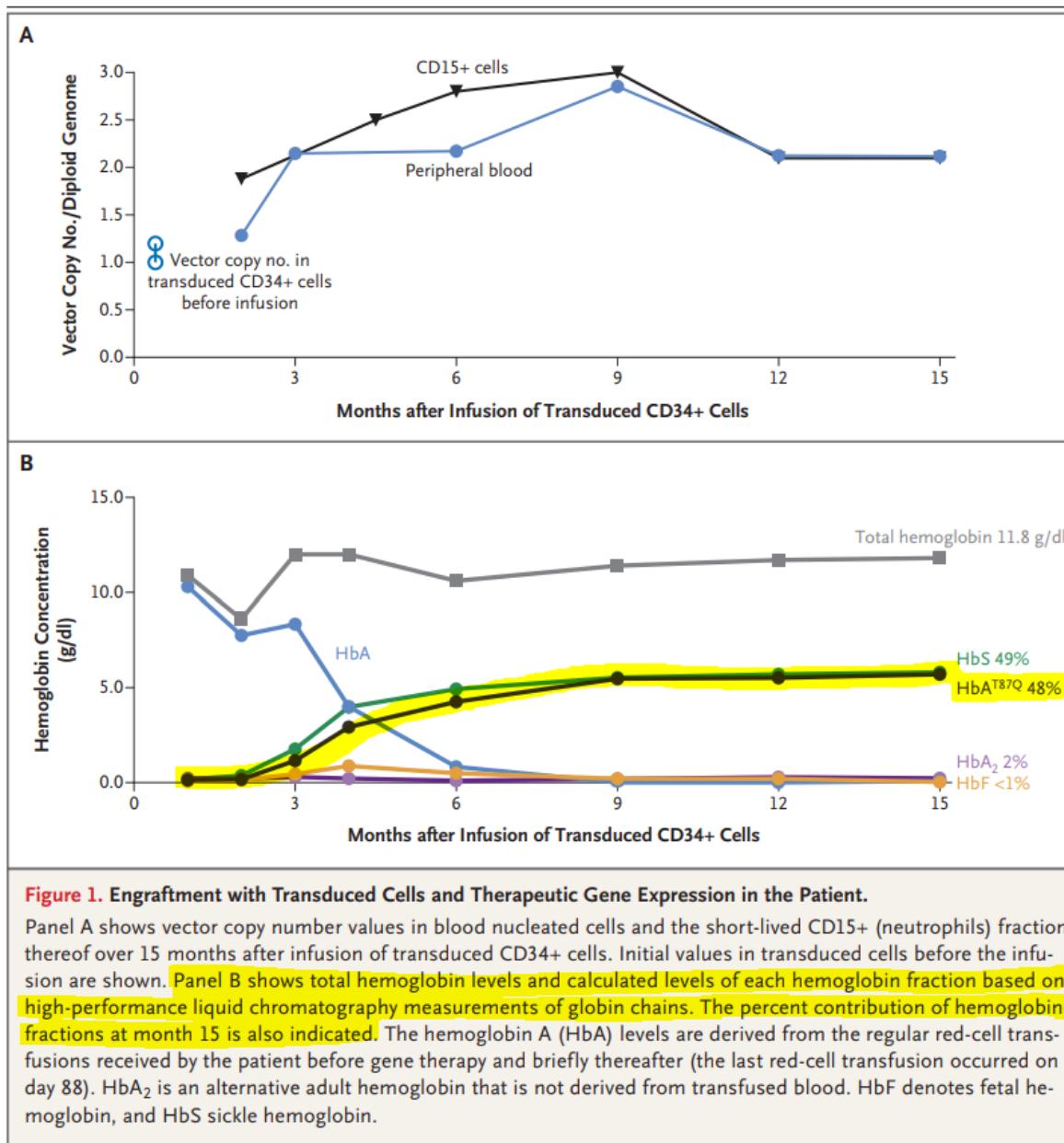
## EXHIBIT M

U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p>The diagram illustrates the BB305 lentiviral vector's genome map. A horizontal line represents the vector at 2000 bp. Vertical lines indicate restriction enzyme cleavage sites. Key sites include (0) <b>Start</b>, (186) <b>SacI - BanII</b>, (308) <b>BamHI</b>, (321) <b>SacI - BanII</b>, (559) <b>StuI</b>, (955) <b>SacI - BanII</b>, (1157) <b>BanII</b>, (1388) <b>BanII</b>, (1708) <b>SpeI</b>, (2203) <b>SacI - BanII</b>, (2236) <b>BstXI</b>, (2352) <b>XbaI</b>, (2411) <b>SphI</b>, (274) (3251). A red box highlights the <b>HS4_BB</b> region, and a blue box highlights the <b>HS4_Plotkin</b> region.</p>
1.8	said vector providing expression of the globin in a mammal <i>in vivo</i> .	<p>Thus, a POSA would understand from this analysis and their own general knowledge that the HS4 fragment within the BB305 vector is highly similar to the HS4 fragment as described in the Plotkin Declaration because their DNA sequences significantly overlap.</p> <p>Accordingly, a POSA would understand that the HS4 sequence within the BB305 vector is equivalent to the limitation “and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR,” (e.g., the HS4 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector.</p> <p>The BB305 vector meets the claim limitation “said vector providing expression of the globin in a mammal <i>in vivo</i>.”</p> <p><u>Exemplary support:</u></p> <p><i>See e.g.</i>, Ribeil 2017, which describes the results of gene therapy with the BB305 vector as follows:</p>

## EXHIBIT M

U.S. Patent No. 8,058,061	BB305 lentiviral vector (hereafter “the BB305 vector”)
	<p><i>“We describe our first patient treated with lentiviral vector-mediated addition of an antisickling <math>\beta</math>-globin gene into autologous hematopoietic stem cells. Adverse events were consistent with busulfan conditioning. Fifteen months after treatment, the level of therapeutic antisickling <math>\beta</math>-globin remained high (approximately 50% of <math>\beta</math>-like-globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease.</i> (Funded by Bluebird Bio and others; HGB-205 ClinicalTrials.gov number, NCT02151526).”</p> <p>Ribeil 2017, at 848 (abstract).</p> <p><b>“RESULTS . . .</b></p> <p><i>Figure 1B shows production of <math>HbA^{T87Q}</math>. . . . <math>HbA^{T87Q}</math> levels also increased steadily (Fig. 1B) and red-cell transfusions were discontinued, with the last transfusion on day 88. Levels of <math>HbA^{T87Q}</math> reached 5.5 g per deciliter (46%) at month 9 and continued to increase to 5.7 g per deciliter (48%) at month 15, with a reciprocal decrease in <math>HbS</math> levels to 5.5 g per deciliter (46%) at month 9 and 5.8 g per deciliter (49%) at month 15. Total hemoglobin levels were stable between 10.6 and 12.0 g per deciliter after post-transplantation month 6. . . .”</i></p> <p><i>Id.</i> at 850-51 (italics and emphasis added) (Figure 1 is reproduced on the following page).</p>

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## EXHIBIT M

U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<p><i>“In the current study, a high concentration of therapeutic HbA<sup>T87Q</sup> (ratio of HbA<sup>T87Q</sup> to HbS, approximately 1) was achieved.<sup>10,11</sup> HbA<sup>T87Q</sup> expression appears to be sufficient to suppress hemolysis, resulting in stable hemoglobin concentrations of 11 to 12 g per deciliter and major improvement in all measurable sickle cell disease-specific biologic markers and blocking sickle cell disease-related clinical events.<sup>20,21</sup></i></p> <p>Additional data on LentiGlobin treatment in sickle cell disease is currently being collected in HGB-206, a multicenter, phase 1/2 clinical study in the United States.<sup>19</sup> . . . <i>Outcomes in this patient provide further supportive evidence to our previously reported results of patients who underwent a similar ex vivo gene therapy procedure for β-thalassemia with the same BB305 vector<sup>22,23</sup> or the previous HPV569 vector.<sup>23,24</sup></i> In addition to the patient with sickle cell disease described here, <i>under this same clinical protocol, 4 patients with transfusion-dependent β-thalassemia have received LentiGlobin BB305. These participants had no clinically significant complications and no longer require regular transfusions.<sup>22</sup> These findings are consistent with early results reported with 18 other patients with thalassemia who received LentiGlobin BB305 in clinical study HGB-204.<sup>23</sup> . . .</i></p> <p>Ribeil 2017, at 854 (italics and emphasis added).</p>
2.0	The cell of claim 1,	<p>At least the CD34<sup>+</sup> HSCs described in Ribeil 2017 meet the recited limitations of claim 1.</p> <p><u>Exemplary support:</u> <i>See claims 1.0 to 1.8 supra.</i></p>
2.1	wherein the mammalian hematopoietic progenitor cell or the stem cell is a human cell.	<p>At least the CD34<sup>+</sup> HSCs described in Ribeil 2017 meet the recited limitation “wherein the mammalian hematopoietic progenitor cell or the stem cell is a human cell.”</p> <p><u>Exemplary support:</u> <i>See claims 1.0, 1.1 and 1.8 supra.</i></p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
5.0	The cell of claim 1,	<p>At least the CD34<sup>+</sup> HSCs described in Ribeil 2017 meet the recited limitations of claim 1.</p> <p><u>Exemplary support:</u></p> <p><i>See claims 1.0 to 1.8 supra.</i></p>
5.1	wherein said functional globin is a mutant globin.	<p>At least the CD34<sup>+</sup> HSCs described in Ribeil 2017 meet the recited limitations of claim 1 and the limitation “wherein said functional globin is a mutant globin.”</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.3 supra.</i></p> <p><i>See also, e.g.,</i> Ribeil 2017, which describes the results of gene therapy with the BB305 vector as follows:</p> <p><b><i>We describe our first patient treated with lentiviral vector-mediated addition of an antisickling β-globin gene into autologous hematopoietic stem cells.</i></b> Adverse events were consistent with busulfan conditioning. <b><i>Fifteen months after treatment, the level of therapeutic antisickling β-globin remained high (approximately 50% of β-like-globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease.</i></b> (Funded by Bluebird Bio and others; HGB-205 ClinicalTrials.gov number, NCT02151526.)</p> <p>Ribeil 2017, at 848 (abstract).</p> <p>In view of these and related disclosures in Ribeil 2017 and general knowledge, a POSA would readily understand that the BB305 vector comprises a mutant human β-globin gene (<math>\beta^{A-T87Q}</math>) which results in β-globin chains with antisickling properties.</p>
7.0	The cells of claim 1,	<p>At least the CD34<sup>+</sup> HSCs described in Ribeil 2017 meet the recited limitations of claim 1.</p> <p><u>Exemplary support:</u></p>

## EXHIBIT M

U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
		<i>See claim 1.0 to 1.8 supra.</i>
7.1	wherein said functional globin is a $\beta$ -globin.	<p>At least the CD34<math>^{+}</math> HSCs described in Ribeil 2017 meet the recited limitations of claim 1 and the limitation “wherein said functional globin is a <math>\beta</math>-globin.”</p> <p><u>Exemplary support:</u></p> <p><i>See claim 5.1 supra.</i></p>
8.0	The cell of claim 7,	<p>At least the CD34<math>^{+}</math> HSCs described in Ribeil 2017 meet the recited limitations of claim 7.</p> <p><u>Exemplary support:</u></p> <p><i>See claims 7.0 and 7.1, supra.</i></p>
8.1	wherein said $\beta$ -globin is a human $\beta$ -globin.	<p>At least the CD34<math>^{+}</math> HSCs described in Ribeil 2017 meet the recited limitations of claim 8.0, and the limitation “wherein said <math>\beta</math>-globin is a human <math>\beta</math>-globin.”</p> <p><u>Exemplary support:</u></p> <p><i>See claims 7.0 and 7.1, supra.</i></p>
11.0	A method for making a mammalian hematopoietic progenitor cell or a mammalian stem cell	<p>At least the method of making CD34<math>^{+}</math> HSCs described in Ribeil 2017 meet the limitation of “[a] method for making a mammalian hematopoietic progenitor cell or a mammalian stem cell composition which comprises”.</p> <p><u>Exemplary support:</u></p> <p><i>See claims 1.0 to 1.8, supra.</i></p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
	composition which comprises	
11.1	(a) preparing a recombinant lentiviral vector comprising	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “(a) preparing a recombinant lentiviral vector comprising” because the BB305 vector used therein was first prepared and then used to treat the human patients disclosed therein.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.2, supra.</i></p>
11.2	a nucleic acid encoding a functional globin operably linked to	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “a nucleic acid encoding a functional globin operably linked to” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.3, supra.</i></p>
11.3	a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR),” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.4, supra.</i></p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
	from a human β-globin locus control region (LCR),	
11.4	the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.5, supra.</i></p>
11.5	a BamHI and HindIII, HS3- spanning nucleotide fragment of said LCR,	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR,” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.6, supra.</i></p>
11.6	and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation of “a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See claim 1.7, supra.</i></p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
11.7	said vector providing expression of the globin in a mammal <i>in vivo</i> ;	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation wherein “said vector providing expression of the globin in a mammal <i>in vivo</i>;” because the BB305 vector used therein meets this limitation.</p> <p><u>Exemplary support:</u></p> <p><i>See</i> claim 1.8, <i>supra</i>.</p>
11.8	and (b) obtaining hematopoietic progenitor cells or stem cells from the mammalian individual,	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation “and (b) obtaining hematopoietic progenitor cells or stem cells from the mammalian individual.”</p> <p><u>Exemplary support:</u></p> <p><i>See</i> claims 1.0, 1.1 and 1.8, <i>supra</i>.</p>
11.9	and transducing the cells with the recombinant vector.	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitation “and transducing the cells with the recombinant vector.”</p> <p><u>Exemplary support:</u></p> <p><i>See</i> claims 1.0, 1.1. and 1.8, <i>supra</i>.</p>
15.0	The method of claim 11,	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitations of claim 11.</p> <p><u>Exemplary support:</u></p> <p><i>See</i> claims 11.0 through 11.9, <i>supra</i>.</p>

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U.S. Patent No. 8,058,061		BB305 lentiviral vector (hereafter “the BB305 vector”)
15.1	wherein said functional globin is a human $\beta$ -globin.	<p>At least the method of making CD34<sup>+</sup> HSCs described in Ribeil 2017 meets the limitations of claim 11 and the limitation “wherein said functional globin is a human <math>\beta</math>-globin.”</p> <p><u>Exemplary support:</u></p> <p><i>See claims 11.0 through 11.9, supra.</i></p>

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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that on March 11, 2022, a copy of the foregoing document was served, by email, on the persons listed below:

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